MEALS AND BLOOD PRESSURE IN THE ELDERLY

Experimental studies on postprandial blood pressure reduction

René Jansen

MEALS AND BLOOD PRESSURE IN THE ELDERLY

Experimental studies on postprandial blood pressure reduction

MEALS AND BLOOD PRESSURE IN THE ELDERLY

Experimental studies on postprandial blood pressure reduction

Een wetenschappelijke proeve
op het gebied van de Geneeskunde en tandheelkunde

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN
VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN
IN HET OPENBAAR TE VERDEDIGEN OP
VRIJDAG 2 JUNI 1989 DES NAMIDDAGS TE 3.30 UUR

door

RENEE WILHELMUS MICHIEL MARIA JANSEN
geboren op 24 december 1956 te Apeldoorn

DRUKKERIJ BENDA B.V.

PROMOTOR:
PROF. DR. A. VAN 'T LAAR

CO-REFERENT:
DR. W.H.L. HOEFNAGELS

The studies presented in this thesis were performed in the Department of Medicine, Division of General Internal Medicine (Head: Prof. Dr. A van 't Laar) and in the Department of Geriatric Medicine (Head: Dr. W.H.L. Hoefnagels), University Hospital Nijmegen, Nijmegen, The Netherlands.

These studies were supported by a grant from the Dutch Stimulation Fund for Research of Ageing (SOOM nr. 86-1-205).
Financial support by the Netherlands Heart Foundation, Bayer Nederland BV, Mijdrecht and Sandoz BV, Uden, for the publication of this thesis is gratefully acknowledged.

Voor mijn moeder en
ter herinnering aan mijn vader.

Contents

Introduction

Although it has been reported in 1929 that food may affect blood pressure [1], it has been recognized for only a few years that ingestion of food can substantially lower blood pressure.
Grollman reported that in young healthy subjects, systolic blood pressure slightly rises after the ingestion of food, whereas diastolic blood pressure remains constant or slightly falls [1]. In patients with autonomic dysfunction, Robertson et al found in 1981 a marked fall in both systolic and diastolic blood pressure after a meal [2]. In addition, in 1983 Lipsitz et al evaluated the effects of a meal on systolic blood pressure in institutionalized elderly subjects aged 75 - 98 years and found a decline in systolic blood pressure by 25 mm Hg [3]. These investigators suggested that postprandial reductions in blood pressure may constitute a cause of postprandial syncope. Postprandial hypotension as a clinical problem was first reported in 1977 by Seyer-Hansen [4]. He described a 65 year old man with parkinsonism who suffered of severe dizziness and visual disturbances during almost every meal. In this patient, large falls in blood pressure were measured after a meal and after ingestion of oral glucose. Remarkably, plasma insulin levels were very high after the ingestion of oral glucose.

Postprandial blood pressure reduction

In view of the high frequency of syncopal episodes observed after breakfast in elderly institutionalized patients, Lipsitz and colleagues evaluated the effect of a standardized 384 Kcal breakfast on blood pressure in elderly subjects with and without a history of syncope [3]. By 35 minutes after the meal, mean systolic blood pressure had declined by 25 ± 5 mm Hg in ten elderly subjects with syncope and 24 ± 9 mm Hg in ten elderly subjects without syncope. There was no significant change in pulse rate in both groups of subjects, which suggested an impaired baroreflex compensation for the hypotensive effects of eating. The hypotensive effects of a meal were also studied in healthy elderly subjects who were without apparent cardiovascular disease and not taking any medication with an influence on the cardiovascular system [5]. In this group, with a mean age 80 ± 6 years, blood pressure declined from 151/72 to 139/61 mm Hg at 50 min after the start of a breakfast. Heart rate increased significantly. Lipsitz et al confirmed that blood pressure also declines in healthy elderly people living in the community [6]. In addition, they found that blood pressure reduction after a noon-meal and after breakfast were of a comparable magnitude. Both studies found a significant

inverse correlation between postprandial and baseline blood pressure. In healthy young subjects the ingestion of food has virtually no effect on blood pressure: supine systolic blood pressure remains more or less constant whereas supine diastolic blood pressure slightly decreases [3,5,7,8].

Clinical significance

Falling is among the most serious problems facing the ageing population and may have great consequences for morbidity (hip fractures), mortality and the cost of health care.

With advancing age, there is a progressive decline in homeostatic capacity, so that the elderly have a blunted ability to adapt to hypotensive stress [9]. The superimposition of drugs and disease may further impair blood pressure regulation. Therefore, additional declines in blood pressure after a meal may become clinically important because of dizziness, syncope and falling. Falls related to hypotension are often clinically presented as a syncope [9]. Although postprandial blood pressure reductions are in most cases only modest, it should be noted that in the elderly also minor systemic falls in blood pressure after eating may cause symptoms of cerebral ischemia due to a defect of vascular autoregulation [10].

Syncope, defined as a sudden temporary loss of consciousness associated with loss of postural tone, is a common symptom in elderly people and remains unexplained in 30 - 50% of all cases [11,12]. It has been reported that syncope in the elderly has a one year mortality of 6 - 19% and a two years mortality of 27% [12,13]. The view that syncope may be associated with serious morbidity is supported by a study by Brocklehurst et al who show that nearly 20% of falls resulting in hip fractures in the elderly were due to fainting [14].

In a prospective study among institutionalized elderly people aimed at identifying causes of syncope, Lipsitz et al found that in 31 of 97 syncope patients, the fainting occurred during a meal or within one hour thereafter [11]. In eight of these subjects, with syncope within one hour of eating, hypotension was documented immediately upon fainting. By 60 min after a meal, mean arterial pressure had declined with an average of 26 mm Hg in these patients in contrast to a decline of 9 mm Hg in nonsyncopal elderly controls [15]. Although the clinical significance of postprandial hypotension in the elderly remains to be elucidated, it seems likely that the combination of a decrease in blood pressure after a meal with or without common hypotensive stimuli such as medications, postural change or a valsalva maneuver during voiding, can result in a predisposition to syncope and falls.

Pathophysiology

Several hypotheses have been proposed to explain the pathophysiological mechanisms of postprandial blood pressure reduction in the elderly.

1 Decreased cardiac output

Splanchnic blood pooling after a meal might reduce venous blood return to the heart and thereby decrease stroke volume and cardiac output resulting in a fall in blood pressure. In young subjects it was found that heart rate and cardiac output rise while stroke volume does not change or increase after a meal. Total systemic resistance decreases after a meal but increases were observed in forearm vascular resistance [7,16]. Hoeldtke et al performed a cardiac catheterization in a 70 year old patient with autonomic neuropathy who became dizzy following a meal [17]. Food ingestion caused a profound drop in both systolic and diastolic blood pressure by 40 - 80 mm Hg and a prompt lowering of systemic vascular resistance, but stroke volume and cardiac output remained unchanged. Although it is hazardous to generalize these results from a single patient, it seems likely that the modest postprandial blood pressure decline as seen in healthy elderly subjects is not a result of decreased cardiac output.

2 Autonomic dysfunction

Postprandial hypotension in the elderly might be due to an inadequate sympathetic compensation for the meal induced shifts of blood volume into the splanchnic system, with an attendant decrease in central blood volume

Even in extreme old age, homeostasis may still be maintained under resting conditions, but when the organism is subjected to stress disturbances of physiological balance may readily occur and the time for recovery is usually prolonged [18,19]. Both the neural and endocrine systems play a major role in regulating the reactions of the organism to changes in the environment and it seems likely that impairment in function of the autonomic nervous system makes a major contribution to the decline in efficiency of homeostatic regulation.

However, it still remains controversial whether the function of the autonomic nervous system declines with age. An increase of sympathetic nervous system activity with advancing age has been proposed because of the higher baseline plasma norepinephrine values in the elderly and because of the finding that the number of impulses at the sympathetic nerve endings into the muscles increased with age [20]. In addition to these findings, increased plasma norepinephrine levels have been observed in older subjects during upright posture [21,22,23] as well as following oral glucose ingestion [23] In contrast, another group found that sympathetic nervous system activity in the iris of the eye declined with age [24].

The activity of the sympathetic nervous system with advancing age remains difficult to determine because of many problems complicating the measurements Firstly, the activity of the sympathetic nervous system is mostly derived from changes in plasma norepinephrine Plasma norepinephrine reflects the norepinephrine that reaches the systemic circulation and represents a small fraction of that which is released. Furthermore, both neuronal release and clearance of norepinephrine from plasma are different for most organs as has been demonstrated by

regional norepinephrine turnover studies [25]. Direct microneurography of nerve fascicles, arterial sampling or kinetic studies for regional norepinephrine measurement are not feasible in large groups of elderly subjects. Despite all these handicaps, it was recently concluded that the measurement of venous plasma concentration of norepinephrine provides a useful guide to sympathetic nervous system activity to detect generalized changes [26]. Secondly, it is generally agreed that plasma norepinephrine increases with age, but it remains to be determined whether this is due to a reduced clearance of norepinephrine [26] or to an increased rate of neuronal release [27]. In addition, Hoeldtke et al reported that in the elderly the rate at which norepinephrine enters the circulation is increased, but that norepinephrine production is normal [28].

Finally, the response of the target organ not only depends on sympathetic nervous system activity and the concentration of neurotransmitters but also on the reactivity of the receptors since an age-related decrease in β-adrenoreceptor sensitivity has been demonstrated [29]. An important limitation which should be kept in mind is that the sympathetic outflow to all organs is not uniform, and regional, organ-specific increases or decreases in sympathetic nervous system activity can occur with different reflexes and in different disease states [26].

An age related increase of sympathetic nervous system activity may be compensatory to a decline in baroreceptor function [24]. The baroreceptor reflex is an important element in the autonomic control of the circulation and serves to minimize wide fluctuations in blood pressure [30]. An impairment of baroreflex function would result in less tonic inhibition of the vasomotor centre. As a result, efferent signals to the heart and vascular smooth muscle would be altered in order to decrease parasympathetic nervous system activity and increase cardiac and vascular sympathetic nervous system activities, resulting in increased spillover of norepinephrine into plasma. Therefore it has been postulated that ageing in man may be accompanied by a generalized decrease of autonomic nervous system function, but that an impaired baroreceptor mechanism leads to a compensatory increase of cardiovascular sympathetic nervous system activity, which masks the underlying functional defect [24].

Age and hypertension reduce baroreflex sensitivity independently of each other [31,32,33]. On top of that, insulin secretion following a meal may play a role by blunting baroreflex activity [34]. Changes at any site in the baroreflex arch, including the loss of arterial distensibility as a consequence of higher blood pressure as well as age, can account for the reduced baroreflex sensitivity [19,32]. Since both ageing and hypertension are associated with impaired baroreflex function, hypertensive elderly may have greater impairments in baroreflex function and therefore greater postprandial declines in blood pressure. Indeed, the relationship between baseline blood pressure and the decrease in blood pressure after a meal supports this suggestion [5,6].

3 Insulin

Meal related insulin release may play a role in postprandial hypotension. Insulin has been recognized to exert cardiovascular effects, even in the absence of hypoglycemia. In diabetic patients with autonomic neuropathy systolic and diastolic blood pressure fell considerably after insulin administration [35,36]. This effect was aggravated by tilting to the vertical position. The hypotensive effect of insulin occurs irrespective whether it is administered intravenously, intramuscularly or subcutaneously. In subjects with normal baroreceptor reflexes, however, blood pressure was only slightly affected after intravenous insulin in the supine position, although in the upright position the fall in blood pressure was more marked after insulin administration [35]. Also other studies report that in patients with chronic autonomic failure and in diabetic patients, intravenous insulin administration caused a decrease of blood pressure and even hypotension and syncope [4,37,38,39]. In addition, Lipsitz et al found evidence for an association between insulin therapy and syncope in institutionalized elderly subjects [11]. In this study it was shown that insulin therapy increased the risk of developing syncope by 29%. However, although an independent correlation between insulin therapy and syncope could be demonstrated, no association existed between insulin therapy and meal-related syncope.

Several studies demonstrated that insulin infusions in conscious dogs resulted in a vasodilator effect on skeletal muscle vasculature [40,41]. In addition, intra-arterial infusion of insulin in the forearm of healthy young volunteers causes an increase in forearm blood flow and a decrease in forearm vascular resistance [42]. A possible explanation for the vasodilation could be an antagonistic action of insulin and norepinephrine. In several studies, insulin has been found to inhibit the vasoconstriction induced by norepinephrine [43,44,45], and to facilitate the re-uptake of norepinephrine at the nerve terminals [46].

On the other hand, insulin infusion increases sympathetic nervous system activity in the absence of changes in blood glucose in young volunteers [47], in diabetic patients without neuropathy [48] and in dogs [40]. In the elderly, however, no change in norepinephrine, as a measure of sympathetic nervous system activity, was found in response to insulin [49] and it was therefore suggested that postprandial hypotension may in part reflect a failure of sympathetic nervous system activation [3]. A decreased stimulation of the sympathetic nervous system by insulin was also found in diabetic patients with autonomic neuropathy [48]. This seems to support the aforementioned hypothesis.

Finally, eating may affect blood pressure homeostasis in the elderly through insulin-induced blunting of baroreflex sensitivity [3]. This suggestion was based on the findings of Appenzeller et al who found that oral glucose decreased baroreceptor response to the Valsalva manoeuver in young and old patients with cerebrovascular disease or peripheral neuropathy [34]. Additional support for a decreased sensitivity of baroreceptor function by insulin was derived from some other studies [35,36]. Miles et al demonstrated that head-up tilting after intrave-

nous insulin administration in normal and diabetic subjects resulted in a greater fall in mean arterial pressure than during tilting without insulin [35]. Similar results were found by Page et al who studied diabetic patients with autonomic neuropathy [36]. Although baroreflex sensitivity was not measured in these studies, Lipsitz et al concluded that insulin administration impaired baroreflex mechanisms [3].

4 Vasodilating hormones

Food ingestion may stimulate the secretion of gastrointestinal vasoactive hormones or substances which may affect blood pressure. In elderly subjects, with insufficient compensatory mechanisms of the sympathetic nervous system, the effects on systemic circulation may become apparent by a decrease of blood pressure. On the other hand, the secretion of gastrointestinal hormones may increase with advancing age or disease. This has, for instance, been demonstrated for pancreatic polypeptide of which the level was significantly higher in the elderly than in young subjects after an oral glucose load [50]. In addition, neurotensin levels rose to a greater extent after a meal in patients with autonomic failure than in young healthy subjects [16]. There may, therefore, be a role for gut peptides in postprandial blood pressure reduction, although this effect may be limited to local or regional effects, i.e. splanchnic vasodilation. Indeed, attenuation or even prevention of postprandial hypotension has been demonstrated with somatostatin [51], which inhibits the secretion of almost all gastrointestinal hormones [52]. Also other vasodilating substances may be involved in the postprandial fall of blood pressure. It has been shown that both indomethacin and caffeine attenuated the blood pressure reduction following a meal in patients with autonomic failure [2,53]. Indomethacin inhibits prostaglandin synthesis and the effect of caffeine may be due to antagonism of an adenosine-mediated vasodilation.

5 Contraction in plasma volume

Another theory, that has been offered to explain postprandial blood pressure reduction, is a shift of water and electrolytes to the lumen of the small intestine induced by hyperosmolar food with subsequent hemoconcentration and decreased circulating blood volume. Furthermore, Gunderson and Christensen showed that intravenous insulin resulted in a decrease of plasma volume [54]. However, this hypothesis seems rather unlikely since Bannister et al have shown that in patients with autonomic failure the hematocrit remains unchanged after a breakfast, suggesting that a contraction in plasma volume is unlikely to be responsible [55]. In addition, there are no changes in plasma electrolytes or osmolality [55]. This suggests that fluid loss, especially into the gut as a result of osmotic changes, is unlikely to contribute to the hypotension.

In conclusion, it may be supposed that one or more of the aforementioned mechanisms are involved in postprandial blood pressure reduction, but the relative

importance of these factors to the pathophysiology of this phenomenon remains unknown.

Outline of the studies

Postprandial blood pressure reduction is associated with age and hypertension. Because many elderly patients are treated with antihypertensive drugs, we wondered whether these drugs may increase the postprandial blood pressure reduction, since these drugs interfere with blood pressure homeostasis. Chapter I and II describe studies on the influence of antihypertensive treatment with different drugs on the extent of the postprandial fall in blood pressure.
To elucidate the role of insulin, we studied the effects of oral glucose versus oral fructose loading on blood pressure in young and old subjects with different blood pressure levels. In contrast to glucose, fructose loading elicits only a small increase in plasma insulin levels (chapter III).
To determine whether the hypotensive effect of glucose loading is mediated by gastrointestinal factors or by the vasodilator properties of insulin we compared the effects of oral and intravenous glucose loading on blood pressure (chapter IV).
Since insulin may affect baroreflex function we studied the influence of oral glucose loading on baroreflex sensitivity in the elderly (chapter V).
Whether the postprandial decline in blood pressure is specifically related to the ingestion of carbohydrate and not of fat or protein was investigated in a study described in chapter VI.
Finally, to investigate whether vasoactive gut hormones play a role in the decline of blood pressure after oral glucose loading, we studied the effects of a somatostatin analogue octreotide (SMS 201-995) on the course of blood pressure after oral glucose with and without the administration of insulin (chapter VII and VIII).

References

1. Grollman A. The effect of ingestion of food on cardiac output, pulse rate, blood pressure and oxygen consumption in man. Am J Physiol 1929;89:366-370.
2. Robertson D, Wade D, Robertson RM. Postprandial alterations in cardiovascular hemodynamics in autonomic dysfunctional states. Am J Cardiol 1981;48:1048-1052.
3. Lipsitz LA, Nyqvist RP, Wei JY, Rowe JW. Postprandial reduction in blood pressure in the elderly N Engl J Med 1983,309:81-83.
4. Seyer-Hansen K. Postprandial hypotension. Br Med J 1977;2:1262.
5. Westenend M, Lenders JWM, Thien Th. The course of blood pressure after a meal: a difference between young and elderly subjects. J Hypertension 1985;3(suppl 3):S417-S419.
6. Lipsitz LA, Fullerton KJ. Postprandial blood pressure reduction in healthy elderly. J Am Geriatr Soc 1986;34:267-270
7. Fagan TC, Sawyer PR, Gourley LA, Lee JT, Gaffney TE. Postprandial alterations in hemodynamics and blood pressure in normal subjects Am J Cardiol 1986;58:636-641.

8. deMey C, Brendel E, Meineke I. Postprandial changes in supine and erect heart rate, systemic blood pressure and plasma noradrenaline and renin activity in normal subjects. Eur J Clin Pharmacol 1987;32:471-476.
9. Lipsitz LA. Abnormalities in blood pressure homeostasis that contribute to falls in the elderly in: Clinics in Geriatric Medicine 1985;1:637-648.
10. Wollner L, McCarthy ST, Soper NDW, Macy DJ. Failure of cerebral autoregulation as a cause of brain dysfunction in the elderly. Br Med J 1979,1:1117-1118.
11. Lipsitz LA, Pluchino FC, Wei JY, Rowe JW Syncope in institutionalized elderly: the impact of multiple pathological conditions and situational stress. J Chron Dis 1986;39:619-630.
12. Kapoor W, Snustad D, Peterson J, Wieand HS, Cha R, Karpf M. Syncope in the elderly. Am J Med 1986,80:419-428.
13. Silverstein MD, Singer DE, Mulley AG, Thibault GE, Barnett GO Patients with syncope admitted to medical intensive care units. JAMA 1982;248:1185-1189.
14. Brocklehurst JC, Exton-Smith AN, Lempert Barber SM, et al. Fracture of the femur in old age: A two-centre study of associated clinical factors and the cause of the fall. Age Ageing 1978;7:7-15.
15. Lipsitz LA, Pluchino FC, Wei JY, Minaker KL, Rowe JW. Cardiovascular and norepinephrine responses after meal consumption in elderly (older than 75 years) persons with postprandial hypotension and syncope. Am J Cardiol 1986;58:810-815.
16. Mathias C, da Costa D, Bannister R: Postcibal hypotension in autonomic disorders, in R Bannister (ed): Autonomic failure. A textbook of clinical disorders of the autonomic nervous system. Oxford, Oxford university press, 1988, 367-380.
17. Hoeldtke RD, Carabello B. Hemodynamic changes during food ingestion in a patient with postprandial hypotension. J Am Geriatr Soc 1987;35:354-356.
18. Exton-Smith AN. The autonomic nervous system, in MSJ Pathy (ed): Principles and practice of geriatric medicine 1985, 779-797.
19. Rowe JW, Troen BR. Sympathetic nervous system and aging in man. Endocrine Reviews 1980;1:167-179.
20. Wallin BG, Sundlof G. A quantitative study of muscle nerve sympathetic activity in resting normotensive and hypertensive subjects. Hypertension 1979;1:67-77.
21. Palmer GJ, Ziegler MG, Lake CR: Response of norepinephrine and blood pressure to stress increases with age. J Gerontol 1978;33:482-487.
22. Ziegler MG, Lake CR, Kopin IJ. Plasma noradrenaline increases with age. Nature 1976;261:333-335.
23. Young JB, Rowe JW, Pallota JA, Sparrow D, Landsberg L. Enhanced plasma norepinephrine response to upright posture and oral glucose administration in elderly human subjects Metabolism 1980;29:532-539.
24. Pfeifer MA, Weinberg CR, Cook D, Best JD, Reenan A, Halter JB. Differential changes of autonomic nervous system function with age in man. Am J Med 1983;75:249-257.
25. Esler M, Jennings G, Korner P, Willett I, Dudley F, Hasking G, Anderson W, Lambert G Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. Hypertension 1988;5:86-99.
26. Esler MD, Hasking GJ, Willet IR, Leonard PW, Jennings GL. Noradrenaline release and sympathetic nervous system activity. J Hypertension 1985;3:117-129.
27. Rubin PC, Scott PJW, McLean K, Reid JL. Noradrenaline release and clearance in relation to age and blood pressure in man. Eur J Clin Invest 1982;12:121-125.
28. Hoeldtke RD, Cilmi KM. Effects of aging on catecholamine metabolism. J Clin Endocrinol Metab 1985;60:479-484.
29. Vestal RE, Wood AJ, Shand DG Reduced beta adrenoreceptor sensitivity in the elderly. Clin Pharmacol Ther 1980;27:181-186.
30. Tuck MI. The sympathetic nervous system in essential hypertension. Am Heart J 1986;112:877-893.

31 Gribbin B, Pickering TG, Sleight P, Peto R Effect of age and high blood pressure on baroreflex sensitivity in man Circ Res 1971,29 424-431
32 Shimada K, Kitazumi T, Ogura H, Sadakane N, Ozawa T Differences in age-dependent effects of blood pressure on baroreflex sensitivity between normal and hypertensive subjects Clin Sci 1986,70 489 94
33 McGarry K, Laher M, Fitzgerald D, Horgan J, O'Brien L, O'Malley K Baroreflex function in elderly hypertensives Hypertension 1983, 5 763-766
34 Appenzeller O, Goss JE Glucose and baroreceptor function effects of oral administration of glucose on baroreceptor function in cerebrovascular disease and in other disorders with baroreceptor reflex block Arch Neurol 1970,23 137-146
35 Miles DW, Hayter CJ The effect of intravenous insulin on the circulatory responses to tilting in normal and diabetic subjects with special reference to baroceptor reflex block and atypical hypoglycaemic reactions Clin Sci 1968,34 419-430
36 Page MMcB, Watkins PJ Provocation of postural hypotension by insulin in diabetic autonomic neuropathy Diabetes 1976,25 90-95
37 Mathias CJ, da Costa DF, Fosbraey P, Christensen NJ, Bannister R Hypotensive and seda tive effects of insulin in autonomic failure Br Med J 1987,295 161-163
38 Brown RT, Polinsky RJ, Lee GK, Deeter JA Insulin induced hypotension and neurogenic orthostatic hypotension Neurology 1986,36 1402-1406
39 Takata S, Yamamoto M, Yagi S, Nata Y, Ikeda T, Hattori N Peripheral circulatory effects of insulin in diabetes Angiology 1985,36 110-116
40 Liang C-S, Doherty JU, Faillace R, et al Insulin infusions in conscious dogs Effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines J Clin Invest 1982,69 1321-1336
41 Reikeras O, Gunnes P Effects of high doses of insulin on regional blood flows during acute left ventricular failure in dogs European Heart J 1986,7 992-998
42 Creager MA, Liang CS, Coffman JD Beta adrenergic-mediated vasodilator response to insu lin in the human forearm J Pharmacol Exp Ther 1985,235 709 714
43 Lee JC, Downing SE Fffects of insulin on cardiac muscle contraction and responsiveness to norepinephrine Am J Physiol 1976,230 1360-1365
44 Yagi S, Takata S, Kiyokawa H, Yamamoto M, Noto Y, Ikeda T, Hattori N Fffects of insulin on vasoconstrictive responses to norepinephrine and angiotensin II in rabbit femoral artery and vein Diabetes 1988,37 1064-1067
45 Alexander WD, Oake RJ The effect of insulin on vascular reactivity to norepinephrine Diabetes 1977,26 611-614
46 Bhagat B, Burke WJ, Dhalla NS Insulin-induced enhancement of uptake of noradrenaline in atrial strips Br J Pharmacol 1981,74 325 332
47 Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta JA, Landsberg L Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man Diabetes 1981,30 219-225
48 Yagi S, Takata S, Yamamoto M, Iwase N, Maeno K, Igarashi A, Noto Y, Ikeda T, Hattori N Effects of insulin on systemic and peripheral circulation and plasma noradrenaline Jpn Circ J 1985, 49 894
49 Minaker KI , Rowe JW, Young JB, Sparrow D, Pallotta JA, I andsberg L Effect of age on insulin stimulation of sympathetic nervous system activity in man Metabolism 1982,31 181-184
50 McConnell JG, Alam MJ, O'Hare MMT, Buchanan KD, Stout RW The effect of age and sex on the response of enteropancreatic polypeptides to oral glucose Age Ageing 1983,12 54-62
51 Hoeldtke RD, O'Dorisio 1M, Boden G Prevention of postprandial hypotension with somatostatin Annals of Internal Med 1985,103 889-890
52 Williams G, Fuessl H, Kraenzlin M, Bloom SR Postprandial effects of SMS 201-995 on gut hormones and glucose tolerance Scand J Gastroenterol 1986,21(suppl 119) 73 83

53. Onrot J, Goldberg MR, Biaggioni I, Hollister AS, Kincaid D, Robertson D. Hemodynamic and humoral effects of caffeine in autonomic failure: Therapeutic implications for postprandial hypotension. N Engl J Med 1985;313:549-554.
54. Gundersen HJG, Christensen NJ. Intravenous insulin causing loss of intravascular water and albumin and increased adrenergic nervous activity in diabetics. Diabetes 1977;26:551-557.
55. Bannister R, Christensen NJ, da Costa DF, Mathias CJ, Wright H, Ukachii-Lois J. Mechanisms of postprandial hypotension in autonomic failure. J Physiol 1984;349:67P.

CHAPTER I

Antihypertensive treatment and postprandial blood pressure reduction in the elderly

R.W.M.M. Jansen, MD, J.W.M. Lenders, MD, Th. Thien, MD, and W.H.L. Hoefnagels, MD.

Department of Medicine, Division of General Internal Medicine, St. Radboud Hospital, University of Nijmegen, The Netherlands.

Gerontology 1987;33:363-368.

CHAPTER I

Antihypertensive treatment and postprandial blood pressure reduction in the elderly

Abstract

Recently it has been demonstrated that blood pressure in the elderly decreases after a meal. To evaluate the influence of antihypertensive treatment on postprandial blood pressure reduction in the elderly, the effects of a breakfast (405 kcal) on blood pressure and heart rate were studied in 15 healthy normotensive elderly subjects (mean age 79.5 ± 6.0 years), in 10 healthy hypertensive elderly subjects (mean age 80.2 ± 5.7 years) and in 22 hypertensive elderly subjects (mean age 71.4 ± 5.0 years) treated with antihypertensive medication (diuretics, β-blockers, vasodilators). In the three groups there was a fall of mean arterial blood pressure of 9.3 ± 1.9%, 13.8 ± 1.9% and 7.9 ± 1.3%, respectively, at 40 min after the start of the breakfast. In all three groups heart rate increased significantly. It is concluded that antihypertensive treatment with the regimens used in this study does not induce an additional fall of blood pressure postprandially. However, the influence of eating should be avoided in the assessment of antihypertensive drug effects in the elderly.

Introduction

Recently it has been demonstrated that elderly subjects frequently show a fall in blood pressure (BP) after a meal. This was found both in ill institutionalized patients on long-term medication [6] and in healthy noninstitutionalized subjects, not taking any medication with an influence on the cardiovascular system [5,8]. In healthy young subjects, BP remains unchanged after a meal [8].
Treatment with antihypertensive drugs may cause an exacerbation of the postprandial BP reduction in the elderly, since these drugs interfere with BP homeostasis [3,4]. Therefore, we studied the effects of a meal on BP and heart rate in healthy elderly people who were treated with various types of antihypertensive drugs.

Subjects and Methods

For this study 22 elderly patients with antihypertensive treatment (Eld-med) were

randomly selected from the outpatient clinic of the Department of Medicine of the St. Radboud University Hospital, Nijmegen.

All patients were over 65 years, healthy and living independently in the community. Patients with the following diseases were excluded from the study: myocardial infarction, congestive heart failure, cerebrovascular accident, diabetes mellitus, chronic respiratory disease, malignancy and mental deterioration. All patients were on hypertensive treatment. Seven patients used a diuretic (hydrochlorothiazide, dose range 25-50 mg, or a combination of hydrochlorothiazide and amiloride), 7 patients used a β-blocker (metoprolol, dose range 50-200 mg; propranolol, dose 320 mg; atenolol, dose range 50-100 mg; or oxprenolol, dose 320 mg) and 8 patients used a combination of diuretics and β-blockers with (n=5) or without (n=3) a vasodilator (endralazine, dose 5 mg; captopril, dose 100 mg; or hydralazine, dose range 150-200 mg). There was no difference in the mean age in the three subgroups.

For comparison, 25 apparently healthy elderly subjects over 65 years, without a history of hypertension, were selected from a total of 432 elderly subjects living in the community. Exclusion criteria, as mentioned above, also applied to this group. Ten subjects appeared to have a high BP (BP over 160/95 mm Hg, Eld-HT) determined by measuring BP twice, after 30 min of rest in the supine position. Fifteen subjects had a normal BP (Eld-NT). The characteristics of the three groups are presented in Table 1. The Eld-med were significantly ($p \leq 0.001$) younger than Eld-NT and Eld-HT. The Quetelet indices in the three groups did not differ significantly. BP of Eld-NT were significantly lower than those of Eld-HT and Eld-med ($p \leq 0.001$). BP of Eld-med, presented in Table 1, are the mean values of the measurements at the last two visits at the outpatient clinic before the study. BP of Eld-HT and Eld-med were not significantly different.

All studies were performed in the morning after an overnight fast. The patients on medical treatment did not take their morning medications. BP was measured with an Arteriosonde®and heart rate (HR) was calculated from an ECG-recording.

After 20 min rest in the sitting position two readings of BP and HR after 2 min in the standing position were collected. After a further 5 min rest three sitting BP and HR readings were collected and the average was taken as the basal standing and sitting BP and HR. Then, at t 0 min, a breakfast of 405 kcal (1,700 kJ) consisting of bread, butter, cheese, oatmeal porridge and orange juice (total 49 g carbohydrate, 17.5 g fat and 13.4 g protein) was consumed during 15 min. BP and HR were measured twice at 20, 25, 30, 35, 40, 45, 50 and 55 min after the start of the meal and the averages of the two readings were used for analysis. After this period in the sitting position again two measurements were taken in the standing position.

For statistical analysis all data were entered on a VAX II/780 computer and analyzed using statistical analysis system (SAS Inc., Cary, N.C.). Student's t test for paired and unpaired observations was used. Correlation coefficients were calculated according to Pearson. Mean arterial pressure (MAP) was calculated as the sum

Table 1 Clinical characteristics of the Eld-NT, the Eld-HT and the Eld-med (mean ± SD).

	Eld-NT (n=15)	Eld-HT (n=10)	Eld-med (n=22)
Sex (male/female)	4 / 11	5 / 5	9 / 13
Age (years) mean	79.5±6.0	80.2±5.7	71.4±5.0
range	71–90	71–90	65–84
Quetelet (kg/m^2)	27.2±4.3	26.6±3.6	26.4±2.9
BP (mm Hg)	139/77±14/8	174/102±31/10	160/88±18/6

of diastolic BP and one third of pulse pressure. All results are given as mean ± SEM, unless indicated otherwise.

Results

After the breakfast, MAP decreased and heart rate increased in each of the three groups, reaching statistical significance at each time point from 20 to 45 min (Fig 1). Results at 40 min, when the maximum effects were observed, are presented here. The Eld-NT had a 5% decrease in systolic BP (142 ± 6 to 134 ± 5 mm Hg, $p \leq 0.01$) and a 12% decrease of diastolic BP (66 ± 2 to 57 ± 2 mm Hg, $p \leq 0.003$). The Eld-HT had a 10% decrease of systolic BP (165 ± 7 to 148 ± 7 mm Hg, $p \leq 0.01$) and a 18% decrease of diastolic BP (82 ± 4 to 68 ± 3 mm Hg, $p \leq 0.001$). In the Eld-med, the BP course did not show an exaggerated fall as compared to the postprandial decrease in BP in Eld-NT and Eld-HT. Systolic BP in Eld-med decreased by 5% (152 ± 4 to 145 ± 4 mm Hg, $p \leq 0.001$) and diastolic BP decreased with 11% (85 ± 2 to 76 ± 2 mm Hg, $p \leq 0.001$).

Fig 2 shows the fall of MAP after the breakfast in the 3 subgroups of patients with different antihypertensive regimens. The postprandial MAP reductions in patients on a diuretic (−7%, −7 mm Hg, n=7), a β-blocker (−10%, −12 mm Hg, n=7) or combination therapy (− 6%, −7 mm Hg, n=8) were not significantly different. None of the patients in either treatment group had a potentially dangerous fall of BP. The greatest fall of MAP was 25 mm Hg (21%), observed in a patient who used a β-blocker.

The increments of HR in Eld-NT (+ 4 ± 3 bpm), in Eld-HT (+ 6 ± 4 bpm) and in the Eld-med (+ 7 ± 1 bpm) did not differ significantly. The increase of BP and HR after assuming the upright position before and after the breakfast is demonstrated in Table 2. Neither before, nor after the meal, did any of the subjects have an orthostatic fall of systolic BP of more than 20 mm Hg. Before, but not after the

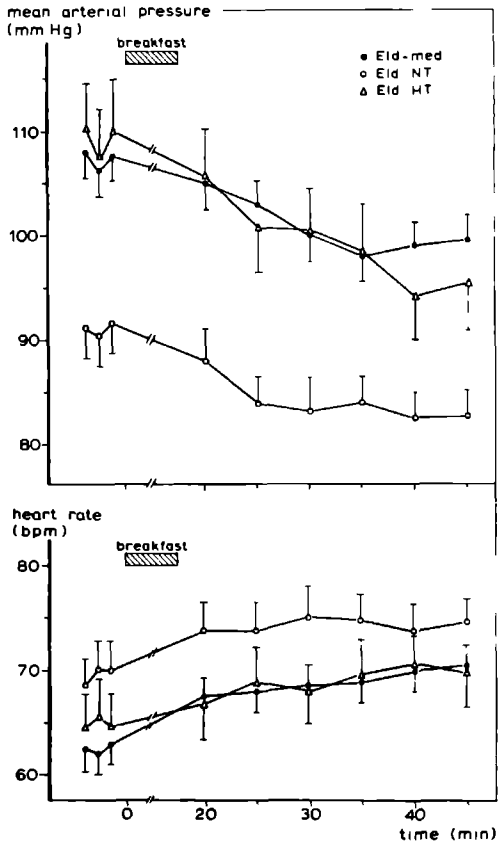

Figure 1 MAP and heart rate before and after the breakfast in Eld-NT (circles), Eld-HT (open triangels) and Eld-Med (dots).

Table 2 Changes (△) in MAP and heart rate induced by assuming the upright position in Eld-NT, Eld-HT and in Eld-med both before and after a standardized breakfast.

	△Mean arterial pressure (mm Hg)			△Heart Rate (bpm)		
	before breakfast		after breakfast	before breakfast		after breakfast
Eld-NT	+12 4±1 7	NS	+8 7±0 9	+11 7±1 4	NS	+10 0±1.2
Eld-HT	+ 6 2±2 1	NS	+9 0±2 1	+10 5±2 3	NS	+ 8 9±1 5
Eld-med	+ 4 0±1 3++	NS	+6 8±0 7	+ 8 3±1 7	NS	+ 8 8±1 0

+ $p \leq 0.05$ when compared with Eld-NT
++ $p \leq 0.001$ when compared with Eld-NT
NS = not significant

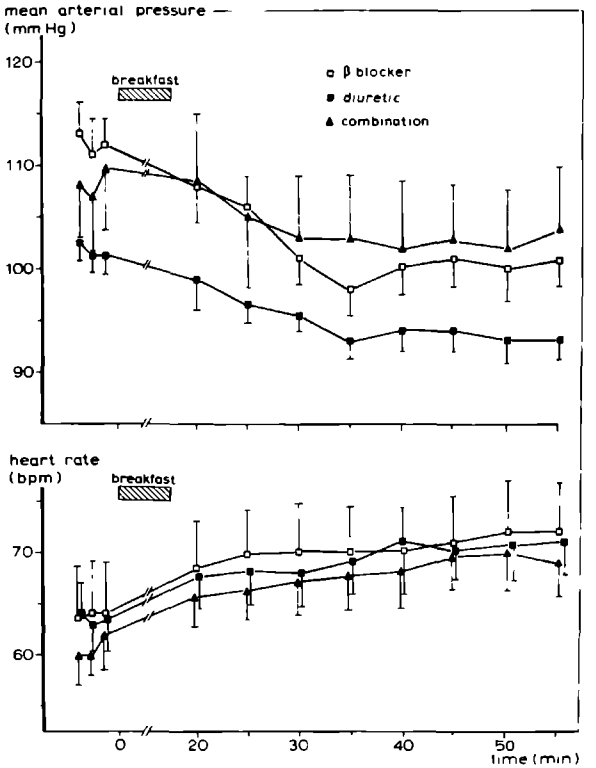

Figure 2 MAP and heart rate before and after the breakfast in elderly hypertensives treated with a ß-blocker (open square), a diuretic (closed square) or combination therapy (closed triangle).

breakfast a significant difference was found in the increase of MAP on standing, between Eld-NT and Eld-HT ($p \leq 0.05$) and between Eld-NT and Eld-med $p \leq 0.001$).
Within the total group there was a significant correlation between the decrease in MAP at 40 min after the meal and the preprandial MAP ($r = -0.42$, $p \leq 0.01$, $n = 47$). The decrease in BP was not related to Quetelet index or to sex.

Discussion

This study confirms and extends the knowledge on the phenomenon of postprandial BP reduction in the elderly [5,6,8]. The fall of BP after a meal may have important clinical implications, especially in the elderly hypertensive patients who are treated with antihypertensive drugs. Our first concern was a possible exaggerated fall of BP after a meal in elderly treated with antihypertensives. The

mechanism of postprandial BP reduction is still unknown, but it has been suggested that an impaired baroreflex may play an important role [6] since both age and hypertension are related to a decrease in baroreflex sensitivity [2]. An exaggerated fall might be expected from a further attenuation of baroreflex function by superimposition of medication Robertson et al [7], studying the effects of a meal in patients with autonomic dysfunction, found a decline of MAP of about 34 mm Hg in 6 patients who were treated with propranolol in contrast to a decline of about 20 mm Hg during placebo. In our study, however, we found that elderly patients on different types of antihypertensive treatment had a similar postprandial BP reduction as hypertensive elderly without medication, although it has to be emphasized that the subjects in the former group were significantly younger. Secondly, postprandial BP reduction may interfere with the assessment of the effectiveness of antihypertensive treatment [1] This may lead to an overestimation of the drug-induced decrease in BP. Indeed, we found in elderly hypertensives treated with various antihypertensive drugs a 5% fall of systolic and an 11% fall of diastolic BP at 40 min after a breakfast. Therefore, the ingestion of food should be avoided during the evaluation of antihypertensive drug effects

In all groups BP increased on standing, both before and after the breakfast. The magnitude of the BP increment when standing was not influenced by the test meal. The increase in BP in response to the upright position before the breakfast was significantly greater in the normotensives than in the hypertensives (with or without medication), probably reflecting a relative impairment of baroreflex in the latter groups It is remarkable, however, that standing BP increments after the meal did not differ significantly in the three groups. Moreover, heart rates in the three groups increased after the meal and on standing, demonstrating that the baroreflex-mediated response to these stimuli was at least not severely impaired. Yet, it might be that the degree of cardioacceleration was inadequate to prevent a postprandial BP reduction.

A few precautions have to be taken into account with respect to the conclusion that antihypertensive treatment does not contribute to an additional fall of postprandial BP in the elderly Firstly, antihypertensive drugs with a central action on the sympathetic nervous system were not investigated in this study. Secondly, it might be that patients with orthostatic hypotension during antihypertensive medication, who were not included in this study, are more susceptible to postprandial BP reductions Thirdly, most of our hypertensive patients (with or without medication) had only mildly elevated BP. This may be of specific importance since we found that postprandial BP reduction is related to basal BP Finally, the conclusion does not apply to antihypertensive drug treatment in very old people

Acknowledgement

We are indebted to Anky Verweijen for assistance in preparing the manuscript.

References

1 Fagan TC, Conrad KA, Mar JH, Nelson L. Effects of meals on hemodynamics: Implications for antihypertensive drug studies. Clin Pharmacol Ther 1986;39 255-260.
2 Gribbin B, Pickering ThG, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 1971;29:424-431
3. Kapoor W, Snustad D, Peterson J, Wieand HS, Cha R, Karpf M. Syncope in the elderly Am J Med 1986,80 419-428
4. Lipsitz LA. Syncope in the elderly. Ann Intern Med 1983,99 92-105
5 Lipsitz LA, Fullerton KJ Postprandial blood pressure reduction in healthy elderly. J Am Geriatr Soc 1986;34:267-270
6. Lipsitz LA, Nyquist RP, Wei JY, Rowe JW. Postprandial reduction in blood pressure in the elderly N Engl J Med 1983;309.81-83
7. Robertson D, Wack D, Robertson RM Postprandial alterations in cardiovascular hemodynamics in autonomic dysfunctional states Am J Cardiol 1981,48:1048-1052.
8. Westenend M, Lenders JWM, Thien Th The course of blood pressure after a meal: a difference between young and elderly subjects J Hypertension 1985,3(suppl 3).S417-S419

CHAPTER II

Effects of nitrendipine and hydrochlorothiazide on postprandial blood pressure reduction and carbohydrate metabolism in hypertensive patients over 70 years of age

René W.M.M. Jansen, MD, Henk J.J. van Lier, MSc, Willibrord H.L., Hoefnagels, MD.

Department of Medicine, Division of General Internal Medicine, University Hospital Nijmegen and Department of Statistical Consultation, University of Nijmegen, The Netherlands.

J Cardiovasc Pharmacol 1988;12(Suppl 4):S59-S63.

CHAPTER II

Effects of nitrendipine and hydrochlorothiazide on postprandial blood pressure reduction and carbohydrate metabolism in hypertensive patients over 70 years of age

Abstract

Recently, it has been recognized that blood pressure (BP) in the elderly may decrease after a meal or oral glucose loading Calcium antagonists and diuretics have been advocated as first-line drugs for the treatment of hypertension in the elderly It is not known whether these antihypertensive drugs may further deteriorate or improve BP homeostasis after a meal Therefore, we studied in a double-blind parallel study the effects of a 12 week treatment with nitrendipine, 20 mg once daily, and hydrochlorothiazide, 50 mg once daily, on BP homeostasis after an oral glucose loading In addition, the effects of both agents on carbohydrate metabolism were studied Before treatment, mean BP decreased by 13 ± 1 mm Hg (SFM) (10%, $p \leq 0.001$) 60 min after the glucose loading in the nitrendipine group (n=9, age 73 ± 3 (SD) years) and by 9 ± 2 mm Hg (SLM) (7%, $p \leq 0.01$) in the hydrochlorothiazide group (n=13, age 76 ± 4 (SD) years) After 12 weeks of treatment, oral glucose loading resulted in mean BP reductions of 7 ± 2 mm Hg (6%, $p \leq 0.01$) and 4 ± 2 mm Hg (4%, not significant) in the nitrendipine and hydrochlorothiazide groups, respectively In the hydrochlorothiazide group, the area under the curve of plasma glucose was significantly higher after treatment than before ($p = 0.03$) We conclude that antihypertensive treatment with nitrendipine or hydrochlorothiazide improves BP homeostasis after an oral glucose loading In contrast to nitrendipine, 12 weeks of treatment with hydrochlorothiazide slightly impairs carbohydrate metabolism

Introduction

Recently, it has been recognized, that blood pressure (BP) in elderly subjects decreases after a meal [1,2] or oral glucose loading [3] The magnitude of this postprandial BP reduction is correlated to basal BP and age [1,2] We found that antihypertensive treatment with diuretics, β-blockers, vasodilators, or a combination of these drugs in the elderly did not cause a further decrease after a meal [4] The

present study was designed to investigate whether antihypertensive treatment actually may improve postprandial BP homeostasis in hypertensive elderly Since both calcium antagonists and diuretics have been advocated as first-line drugs in the treatment of hypertensive elderly, we studied the effects of a 12-week treatment with the new long-acting calcium antagonist nitrendipine and the diuretic hydrochlorothiazide on postprandial BP reduction in patients over 70 years of age In addition, the effects of either therapy on carbohydrate metabolism were studied

Patients and Methods

In a double-blind, randomized, parallel-group clinical trial, the hemodynamic and metabolic effects of 12 weeks of treatment with nitrendipine 20 mg once daily given to 15 hypertensive elderly patients were compared to those with hydrochlorothiazide 50 mg once daily given to 16 hypertensive elderly patients Before active treatment, patients received 4 weeks single-blind placebo therapy For the present, study 22 patients were randomly selected Because of technical failures, the oral glucose loading could not be performed in all patients Nine patients were treated with nitrendipine and 13 patients with hydrochlorothiazide All patients were 70 years or older and were enrolled in the study if they had, after a washout period of 10 weeks, a mean supine diastolic BP of 95 to 120 mm Hg or a mean systolic BP of 180 mm Hg or more, measured at three consecutive visits Patients with the following medical histories were excluded angina pectoris, congestive heart failure, myocardial infarction, cerebrovascular accident, diabetes mellitus, gout and/or a plasma creatinine concentration of 150 μmol/l or more The clinical characteristics of the two groups are presented in Table 1 They did not differ in age, BP, heart rate and Quetelet index

Table 1 Clinical characteristics of study subjects (mean SD)

		Nitrendipine (n = 9)	Hydrochlorothiazide (n = 13)
Age (years)	mean	73 ± 3	76 ± 4
	range	70 – 78	70 – 84
Sex (male/female)		4 / 5	3 / 10
Quetelet index (kg/m^2)		27 ± 5	27 ± 4
Systolic BP (mm Hg)		187 ± 15	187 ± 17
Diastolic BP (mm Hg)		106 ± 5	102 ± 5
Heart rate (beats/min)		78 ± 14	69 ± 10

In each patient, an oral glucose loading test was performed before and at the end of the treatment period. Prior to these tests, the patients followed a diet rich in carbohydrates for 3 days. All studies were carried out in the morning after an overnight fast and 24 h after drug administration. At time 0 the subjects consumed 75 g glucose in 300 ml water within 5 min. BP (Arteriosonde®) and heart rate (electrocardiogram) were measured in the supine position at regular intervals of 5 min from −20 to 120 minutes. Thirty min before the start of the glucose loading a 21-gauge butterfly was inserted in an antecubital vein and kept patent with physiologic saline. At times 0, 30, 60, 90, and 120 min blood samples were collected for measurement of plasma glucose, insulin (radioimmuno-assay) and plasma catecholamines (radioenzymatic assay [5]).

Statistical comparisons between paired observations were made with Student's t test when appropriate; otherwise Wilcoxon's signed rank test was used. The Mann-Whitney U test was used to compare the groups on quantitative data. In order to reduce the overall probability of a type I error, a level of significance of $p \leq 0.01$ was employed (Bonferroni's correction). Comparison between curves was made with a distribution-free analysis of variance [6]. In this test, a p level of 0.05 or less was considered to be significant. To study the independent effects of age and basal BP on BP responses, a multiple regression analysis was performed. Mean BP was calculated as the sum of diastolic BP and one third of pulse pressure. The area under the curve was calculated by applying the trapezoidal rule. All values given in tables and text are expressed as mean ± SEM, unless indicated otherwise.

Results

The response of BP, heart rate, and plasma norepinephrine to oral glucose loading before and during nitrendipine or hydrochlorothiazide treatment is presented in Table 2 and Fig 1. Both treatments caused a significant fall of BP after 12 weeks of treatment ($p \leq 0.01$). The response of BP to either treatment was not significantly different. After oral glucose loading before treatment, mean BP decrease by 13 + 1 mm Hg (10%, $p \leq 0.001$, t 60 min) in the nitrendipine group and by 9 + 2 mm Hg (7%, $p \leq 0.01$; t 60 min) in the hydrochlorothiazide group. After 12 weeks of treatment, oral glucose loading resulted in mean BP reductions of 7 + 2 mm Hg (6%, $p \leq 0.01$; t 60 min) and 4 + 2 mm Hg (4%, not significant; t 60 min) in the nitrendipine and hydrochlorothiazide groups, respectively. After 12 weeks of treatment, the percentage mean BP changes at 60 min after the glucose loading were significantly lower in both groups when compared with pretreatment values (Fig 2). Comparison between the pre- and posttreatment curves of mean BP reductions revealed only in the nitrendipine group a significant difference ($p = 0.04$). Multiple regression analysis for the total group ($n = 22$) showed that the pretreatment change in mean BP at time 60 min was correlated to basal mean BP

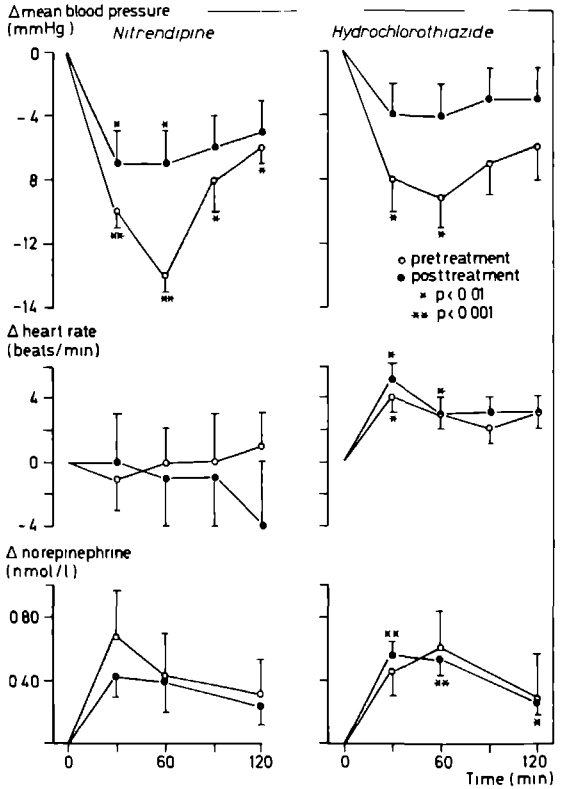

Figure 1 Mean changes of mean blood pressure, heart rate and norepinephrine after oral glucose loading before and after treatment in both groups

(r= −0.51, p=0.02) and age (r= −0 43, p=0 05). In Fig 3, the pretreatment basal mean BP is plotted against the mean BP at 60 min. The plot shows a significant deviation of the regression line in slope (p=0 02) and intercept (p=0 04) from the line of identity, which means that the changes of BP are proportionally related to basal BP.

In both treatment groups, heart rate did not change after 12 weeks of treatment. The influence of oral glucose loading on heart rate was not significantly influenced by treatment in either group (Fig 1) Only in the hydrochlorothiazide group heart rate increased significantly after oral glucose loading before and after treatment. In the nitrendipine group, no change in heart rate could be demonstrated However, comparison between treatment groups revealed no differences in heart rate responses after glucose loading.

Baseline plasma norepinephrine levels were slightly, but insignificantly, lower after treatment in both groups. In the nitrendipine group basal plasma norepinephrine decreased from 2 01 ± 0 40 to 1.77 ± 0.22 nmol/l In the hydrochloro-

Table 2 Effects of oral glucose loading on systolic and diastolic blood pressure before and after 12 weeks of treatment

	Time (min)	Nitrendipine		Hydrochlorothiazide	
		Before	After	Before	After
Systolic BP (mm Hg)	0	174 ± 4	161 ± 4§§	175 ± 6	157 ± 7§§§
	30	163 ± 5§	157 ± 4	169 ± 6	155 ± 6
	60	150 ± 5‘ ‘	154 ± 5	166 ± 5	155 ± 5
	90	165 ± 5	157 ± 5	167 ± 5	156 ± 6
	120	168 ± 5	158 ± 6	169 ± 5	155 ± 5
Diastolic BP (mm Hg)	0	106 ± 2	99 ± 3‘	98 ± 1	89 ± 2§§
	30	96 ± 3 ‘	91 ± 4	89 ± 2	84 ± 2‘
	60	94 ± 2	92 ± 4	89 ± 2‘	84 ± 2‘‘
	90	99 ± 3	93 ± 4‘‘	91 ± 3	85 ± 2
	120	99 + 3	94 ± 4‘‘	92 ± 2‘	85 ± 2

‘ $p \leq 0.01$ and ‘‘ $p \leq 0.001$ compared with baseline values

§ $p \leq 0.05$, §§ $p \leq 0.01$ and §§§ $p \leq 0.001$ compared with pretreatment baseline values

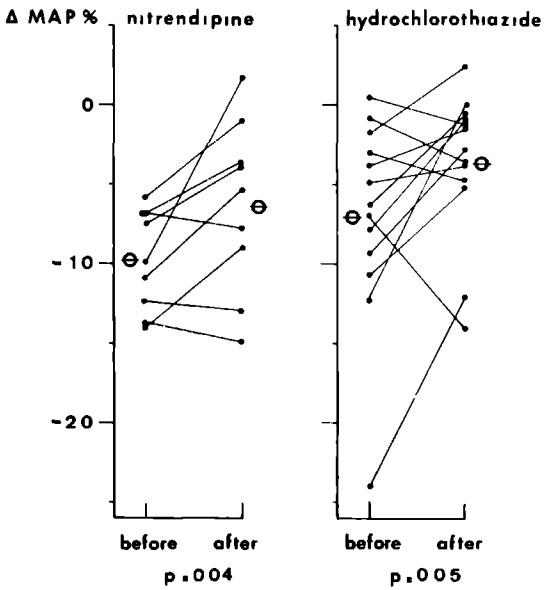

Figure 2 Individual percentage changes of mean blood pressure 60 min after oral glucose loading before and after treatment in both groups.

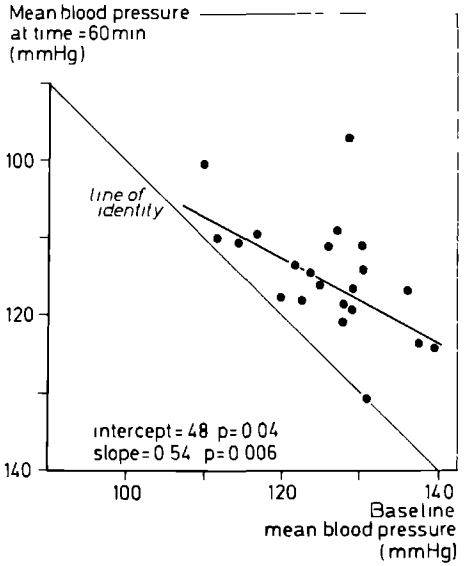

Figure 3 Pretreatment basal mean blood pressure versus pretreatment mean blood pressure 60 min after oral glucose for the total group (n=22)

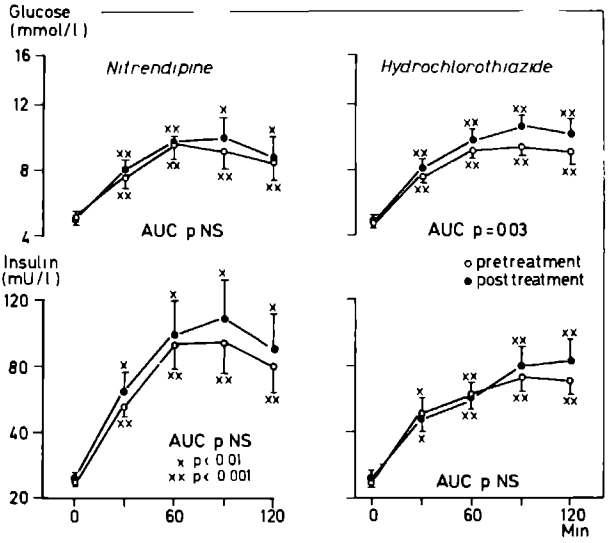

Figure 4 Effects of oral glucose loading on plasma glucose and insulin before and during treatment. AUC means area under the curve. NS means not significant. The p values refer to the significance of the difference between pre- and posttreatment AUC values.

thiazide group basal plasma norepinephrine decreased from 2.00 ± 0.32 nmol/l before treatment to 1.69 ± 0.14 nmol/l after treatment. Before treatment, oral glucose loading resulted in a slight and insignificant increase of plasma norepinephrine in both groups. After treatment, norepinephrine increased significantly in response to oral glucose loading in the hydrochlorothiazide group, but not in the nitrendipine group. However, comparison of plasma norepinephrine responses did not yield any difference between pre- and posttreatment values within or between both groups.

In Fig 4, the curves of glucose and insulin are depicted after glucose loading in each group. Treatment with hydrochlorothiazide resulted in a slight increase of baseline glucose (0.3 ± 0.1 mmol/l, $p=0.06$) and insulin (4 ± 1 mU/l, $p \leq 0.05$), whereas treatment with nitrendipine did not change these parameters. The area under the curve of plasma glucose after oral glucose loading was similar before and after treatment with nitrendipine. In the hydrochlorothiazide group, the area under the curve of plasma glucose was significantly higher after treatment than before ($p=0.03$). The area under the curves of insulin did not change significantly in either group.

Discussion

A decrease of BP after a meal or oral glucose loading has been described before [1,3]. Postprandial BP reduction is an age and BP related phenomenon [1,2]. Elderly hypertensives are the most likely to have postprandial decreases in BP. BP also decreases after an oral glucose loading in elderly persons, dependent on age and basal BP, and comparable in magnitude and time course to the BP reduction after a meal [3,4]. We reported earlier that different types of antihypertensive drugs did not cause a further BP reduction after a meal [4], contrary to what one might have expected based on the well-known interference of these drugs with BP homeostasis in the elderly. Moreover, in the present study we found that after 12 weeks of treatment with nitrendipine or hydrochlorothiazide, the decrease of BP after an oral glucose loading was significantly lower than before treatment, in accordance with our finding in the untreated patients, in whom the mean BP, 60 min after the glucose administration, was proportionally related to the basal mean BP.

The mechanism of postprandial BP reduction is not known, but based on previous studies [3], we suggest that oral glucose loading induces a specific vasodilation of splanchnic vasculature that is, in hypertensive elderly patients, incompletely counterbalanced by activation of the sympathetic nervous system, due to an age and BP related decrease of baroreflex sensitivity [7,8]. A decrease of baroreflex sensitivity in this study is suggested by absent or small changes in heart rate and plasma norepinephrine, in the face of marked BP reductions induced by glucose loading. The fact that not only the absolute but also the percentage fall of BP was

reduced by either antihypertensive treatment might indicate that these treatments cause an improvement of BP homeostatic mechanism Indeed, McI eay et al found after chronic nifedipine therapy not only a resetting of the sinoaortic baroreflex but also an increase in its sensitivity, as was established by the response of heart rate and BP to phenylephrine [9] However, several other studies with nifedipine [10] and nicardipine [11] showed a resetting of baroreflexes without any change in sensitivity In our study, an increase of baroreflex sensitivity after treatment can be derived from the finding that oral glucose loading elicited, despite lower BP reductions than before treatment, heart rate and norepinephrine responses comparable to those before treatment

In this study, we used an oral glucose loading test instead of a meal in order to determine postprandial BP reduction Therefore, we had the opportunity to study at the same time the effects of both treatments on carbohydrate metabolism in the elderly Calcium antagonists may interfere with the second phase of insulin secretion, which depends on a Ca^{2+} influx through the calcium channel [12] Studies of isolated pancreatic islets of Langerhans have shown that nitrendipine and several other types of calcium antagonists cause a dose dependent inhibition of insulin output [13] However, in the present study of nondiabetic elderly hypertensives, no evidence for an influence of nitrendipine on glucose tolerance was found Also, other studies did not found any effect of nitrendipine on plasma glucose or insulin response to oral glucose loading [12,14] In contrast, hydrochlorothiazide treatment caused the well-known impairment of carbohydrate metabolism

In conclusion, our data indicate that antihypertensive treatment with nitrendipine or hydrochlorothiazide in hypertensive patients over 70 years of age improves BP homeostasis after an oral glucose loading In contrast to nitrendipine, 12 weeks of treatment with hydrochlorothiazide slightly impairs carbohydrate metabolism

Acknowledgement

The authors wish to express their gratitude to J Willemsen, I aboratory of Experimental and Chemical Endocrinology of the University Hospital of Nijmegen, who performed the plasma norepinephrine determinations, and to Louise Jagtenberg for preparation of this manuscript

References

1 Lipsitz I A, Nyquist RP, Wei JY, Rowe JW Postprandial reduction in blood pressure in the elderly N Engl J Med 1983,309 81-83

2 Westenend W, I enders JWM, Thien Th The course of blood pressure after a meal a difference between young and elderly subjects J Hypertension 1985,3(suppl 3) S417 S419

3 Jansen RWMM, Penterman BJM, van Lier HJJ, Hoefnagels WHL Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin Am J C ardiol 1987,60 1087 1091

4 Jansen RWMM, I enders JWM, Thien T, Hoefnagels WHI Antihypertensive treatment and postprandial blood pressure reduction in the elderly Gerontology 1987,33.363-368
5. Hoffmann JJML, Willemsen JJ, Lenders JWM, Benraad ThJ Reduced imprecision of the radioenzymatic assay of plasma catecholamines by improving the stability of the internal standard Clin Chim Acta 1986,156.221-226.
6 Koziol JA, Maxwell DA, Fukushima M, Colmerauer MFM, Pilch YH. A distribution-free test for tumor-growth curve analysis with application to an animal tumor immunotherapy experiment. Biometrics 1981;37:383-390.
7. Gribbin B, Pickering TG, Sleight P, Reto R Effect of age and high blood pressure on baroreflex sensitivity in man Circ Res 1971,29·424-431.
8. Shimada K, Kitazumi T, Ogura H, Sadakane N, Ozawa T. Differences in age-dependent effects of blood pressure on baroreflex sensitivity between normal and hypertensive subjects. Clin Sci 1986,70:489-494
9 McLeay RAB, Stallard TJ, Watson RDS, I ittler WA The effect of nifedipine on arterial pressure and reflex cardiac control Circulation 1983,67·1084-1090.
10 Kiowski W, Frne P, Bertel O, Hulthen UL, Ritz R, Buhler FR Unchanged baroreflex sensitivity during acute and chronic antihypertensive therapy with nifedipine J Hypertension 1983;1(suppl 2):365-367.
11 Young MA, Watson RDS, Littler WA Baroreflex setting and sensitivity after acute and chronic nicardipine therapy Clin Sci 1984;66:233-235
12 Trost BN, Weidmann P. Effects of nitrendipine and other calcium antagonists on glucose metabolism in man. J Cardiovasc Pharmacol 1984;6(suppl 7):S986-S995
13. Malaisse WJ, Sener A Calcium antagonists and islet function XII. Comparison between nifedipine and chemically related drugs Biochem Pharmacol 1981;30:1039-1041.
14 Johnson BF, Romero L, Marwaha R. Hemodynamic and metabolic effects of the calcium channal blocking agent nitrendipine Clin Pharmacol Ther 1986,39 389-394

CHAPTER III

Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin

René W.M.M. Jansen, MD, Berry J.M. Penterman, MD, Henk J.J. van Lier, MSc, and Willibrord H.L. Hoefnagels, MD.

Department of Medicine, Division of General Internal Medicine, Sint Radboud University Hospital Nijmegen and Department of Statistical Consultation, University of Nijmegen, The Netherlands.

Am J Cardiol 1987;60:1087-1091.

CHAPTER III

Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin

Abstract

Recently it has been demonstrated that blood pressure (BP) in the elderly may decrease after a meal. The pathophysiologic mechanism of this phenomenon is unknown. It has been suggested that a failure of insulin-mediated sympathetic nervous system activation plays a role. To evaluate the role of endogenous insulin, the effects of oral glucose and oral fructose loading on BP, heart rate and norepinephrine levels were studied in 10 young normotensive volunteers (YN), 10 young hypertensive patients (YH), 10 elderly normotensive volunteers (EN) and 10 elderly hypertensive patients (EH). Fructose, 75 g/300 ml of water, elicited – in contrast to the same amount of glucose – only a small increase in insulin and glucose levels. After glucose loading, mean arterial BP decreased by 17 mm Hg in the EH group ($p \leq 0.001$), 6 mm Hg in the EN group ($p \leq 0.01$), and 7 mm Hg in the YH group ($p \leq 0.001$), and did not change in the YN group. After oral fructose loading, BP did not change in any group. In all groups except the YN group, the increases of norepinephrine level and heart rate after both tests were not significantly different. These findings suggest that the BP reduction after glucose loading is related to glucose-mediated factors. A failure of insulin-mediated sympathetic nervous system activation does not appear to play a major role.

Introduction

Blood pressure (BP) in the elderly has been shown to decrease after a meal. This was found both in frail, institutionalized elderly patients [1] as well as in healthy, community-dwelling elderly persons [2,3]. The clinical significance of this phenomenon is not clear, but in a recent study Lipsitz et al identified 8 elderly patients with meal-related syncope [4]. The mechanism of postprandial BP reduction is unknown. It has been suggested that failure of insulin-mediated sympathetic nervous system activation causes the decrease of BP after a meal [1]. Indeed, sympathetic nervous system activation by intravenous administration of insulin and glucose has been shown to be blunted in the elderly [5] but not in younger persons [6]. However, oral glucose loading induces a greater sympathetic nervous system activation in elderly than in younger persons [7]. To elucidate the role of insulin in

the phenomenon of postprandial BP reduction, we studied the effects of oral glucose loading on the cardiovascular and sympathetic nervous systems in healthy volunteers and in patients of different ages and BP levels.

Methods

Fourty normotensive and hypertensive persons of several age groups participated in this study. The first group consisted of 10 healthy young volunteers with a normal blood pressure (YN). For the second group, 10 young hypertensive patients (YH) were randomly selected from the outpatient clinic. Hypertension was defined as a supine systolic BP ≥160 mm Hg and/or a supine diastolic BP ≥95 mm Hg, measured on 3 occasions using a standard sphygmomanometer. The third group consisted of 10 healthy, community-dwelling, normotensive elderly volunteers older than 70 years (EN). For the fourth group 10 hypertensive patients older than 70 years were randomly selected from the outpatient department (EH). No participant had a history of myocardial infarction, cerebrovascular accident or diabetes mellitus. All patients had uncomplicated essential hypertension and had not taken antihypertensive medication for at least 1 month before the study. Characteristics of the 4 groups are presented in Table 1.

Table 1 Characteristics of study subjects (mean ± standard error of the mean).

	YN (n=10)	YH (n=10)	EN (n=10)	EH (n=10)
Sex (men/women)	6 / 4	6 / 4	4 / 6	4 / 6
Age (years) mean	28± 1	44± 2	75± 2	75± 1
range	23–32	30–51	70–87	71–84
Quetelet index (kg/m^2)	21± 1	25± 1	25± 1	27± 1
Systolic BP (mm Hg)	107± 2	146± 6	152± 2	191± 4
Diastolic BP (mm Hg)	72± 3	101± 4	81± 2	105± 2
Heart Rate (beats/min)	62± 2	74± 3	62± 2	71± 4

$p \leq 0.05$ versus young normotensives
$p \leq 0.05$ versus elderly normotensives

In each subject an oral glucose- and an oral fructose loading test was performed in a random, single-blind order with an interval of 1 week. Before these tests, the participants followed a diet rich in carbohydrates for 3 days. All studies were carried out in the morning after an overnight fast. At time 0 the subjects consumed 75 g of glucose or fructose in 300 ml of water within 5 min. BP (Arteriosonde®) and

heart rate (electrocardiogram) were measured in the supine position at regular intervals of 5 min from −20 to 120 min. A 21 gauge butterfly needle was inserted at time −30 min in an antecubital vein and kept patent with physiologic saline solution. At time 0, 30, 60, 90 and 120 min, blood samples were collected for measurement of glucose, insulin (radioimmuno assay) and norepinephrine levels (radioenzymatic assay [8]).

Statistical comparisons between paired observations were made with a Student t test when appropriate; otherwise Wilcoxon's rank sum test was used. To reduce the overall probability of a type I error, a level of significance of $p \leq 0.01$ was used (Bonferroni's correction). Comparison between curves were made with a distribution-free analysis of variance [9]. In this test a p-value of ≤ 0.05 was considered to be statistically significant. To study the independent effects of age, Quetelet index, basal BP, insulin and glucose on BP responses, a multiple regression analysis was used. Mean arterial pressure was calculated as the sum of diastolic BP and one-third of pulse pressure. All values given in tables and text are expressed as mean ± standard error of the mean.

Results

Tables 2 and 3 present the mean values of mean arterial BP, heart rate, norepinephrine, glucose and insulin in the 4 study groups, both after glucose and after fructose loading. In Fig 1 and 2 the changes of these measurements in each test are shown.

Blood pressure

BP, expressed as mean arterial pressure, decreased significantly in response to glucose loading in YH, EN and EH (Table 2 and 3). After fructose loading, BP remained essentially unchanged in all 4 groups.

Systolic BP decreased by 5 ± 1 mm Hg (from 146 ± 6 to 141 ± 5 mm Hg, $p \leq 0.01$) in the YH group, by 5 ± 3 mm Hg (from 144 ± 6 to 139 ± 7 mm Hg, not significant) in the EN group and by 23 ± 4 mm Hg (from 188 ± 5 to 165 ± 6 mm Hg, $p \leq 0.001$) in the EH group. Diastolic BP decreased by 7 ± 2 mm Hg (from 101 ± 4 to 94 ± 5 mm Hg, $p \leq 0.01$) in the YH group, by 6 ± 1 mm Hg (from 81 ± 2 tot 75 ± 3 mm Hg, $p \leq 0.001$) in the EN group and by 14 ± 2 mm Hg (from 104 ± 3 to 90 ± 3 mm Hg, $p \leq 0.001$) in the EH group.

The decrease of mean arterial BP after glucose loading was significantly greater in the EH group than in the EN and YH groups (Fig 1). BP decreased in every elderly subject (Fig 3). The maximal decrease in BP was in an 84-years-old hypertensive woman who had a 30 mm Hg decrease in mean arterial BP. In no patient did the BP decrease cause subjective symptoms. Regression analysis revealed a dependence on age ($p = 0.07$) and basal systolic BP ($p = 0.05$). Quetelet index, basal diastolic BP and insulin and glucose levels were not significantly correlated with mean arterial BP reduction.

Table 2 Mean values (± standard error of the mean) of mean arterial blood pressure (MAP), heart rate (HR), norepinephrine (NE), glucose and insulin before and after oral fructose (F) or glucose (G) loading in both young groups.

	time (min)	normotensive G	normotensive F	hypertensive G	hypertensive F
MAP	0	85±2	85±2	116±4	115±5
(mm Hg)	30	83±1	87±2	110±5*	115±4
	60	84±1	86±2	111±5	114±3
	90	85±2	87±2	114±5	114±5
	120	87±2	87±2	116±5	115±4
		p=0.09		p=0.03	
HR	0	62±2	62±3	74±3	74±2
(beats/	30	64±2	61±3	80±3	71±2*
minute)	60	63±3	66±3	79±3	76±3
	90	65±3	67±3*	77±3	75±2
	120	64+2	68±3	77±3	77±2
		p=0.55		p=0.06	
NE	0	0.77±0.10	0.76±0.08	1.39±0.18	1.28±0.18
(nmol/l)	30	1.08±0.15	0.92±0.09**	1.91±0.22**	1.60±0.19
	60	1.01±0.14	0.89±0.09*	1.80±0.19**	1.56±0.21
	120	1.03±0.10*	0.83±0.09	1.50±0.13	1.53±0.17
		p=0.02		p=0.09	
Glucose	0	4.1±0.2	4.2±0.1	4.6±0.2	4.5±0.1
(mmol/l)	30	6.9±0.4***	4.7±0.2**	7.9±0.4***	5.0±0.1
	60	6.4±0.5**	4.6±0.2	9.0±0.8***	5.2±0.3
	90	5.1±0.3	4.2±0.2	8.1±0.8	5.0±0.2
	120	4.2±0.3	4.1±0.2	6.7±0.5*	4.7±0.1
		p=0.0027		p=0.0004	
Insulin	0	6± 1	5±1	8± 1	7±1
(mU/l)	30	68±17**	12±2**	44± 6**	13±1*
	60	55±12**	13±1**	57± 6 *	16±1 **
	90	38± 7**	9±1	61± 9**	19±1***
	120	19± 5	8±1	54±10**	12±1*
		p=0.0003		p=0.0004	

* $p \leq 0.01$
** $p \leq 0.001$

Table 3 Mean values (± standard error of the mean) of mean arterial blood pressure (MAP), heart rate (HR), norepinephrine (NE), glucose and insulin before and after oral fructose (F) or glucose (G) loading in both elderly groups

	time (min)	normotensive G	normotensive F	hypertensive G	hypertensive F
MAP	0	102±3	101±3	132±2	130±3
(mm Hg)	30	96±3	106±4	117±3	131±3
	60	96±4	104±4	115±3	128±3
	90	100±4	107±5	120±3	127±3
	120	101±4	106+5	122±3	130±4
		p=0 006		p=0 0001	
HR	0	62±2	63±2	71±4	73±3
(beats/	30	67±2	65±2	75±4	73±3
minute)	60	66±2	66±2	74±3	75±5
	90	67±2	68±2	72±4	76±4
	120	65±2	69±2	75±3	78±5
		p=0 19		p=0 78	
NE	0	1 72±0 18	1 81±0 21	2 28±0 32	2 51±0 31
(nmol/l)	30	2 23±0 10	2 08±0 21	2 79±0 34	2 59±0 32
	60	2 21±0 17	2 26±0 26	2 64±0 30	2 86±0 38
	120	2 08±0 22	2 19±0 31	2 46±0 21	2 58±0 32
		p=0 44		p=0 13	
Glucose	0	4 8±0 1	4 9±0 2	5 0±0 3	4 9±0 3
(mmol/l)	30	7 9±0 5	5 6+0 2	8 3±0 6	5 7±0 3
	60	9 5±0 6	6 1±0 4	10 2±0 7	6 2±0 4
	90	9 2±0 6	5 7±0 3	9 8±0 8	6 1±0 4
	120	8 3±0 6	5 3±0 2	9 3±1 1	6 0±0 5
		p=0 0002		p=0 0005	
Insulin	0	8±1	9±2	11± 2	11±2
(mU/l)	30	39±5	20±1	51± 7	21±4
	60	58±9	21±2	83±16	25±5
	90	57±8	19±2	92±18	24±5
	120	50±7	15±2	80±14	21±4
		p=0 0002		p=0 0003	

p≤0 01
p≤0 001

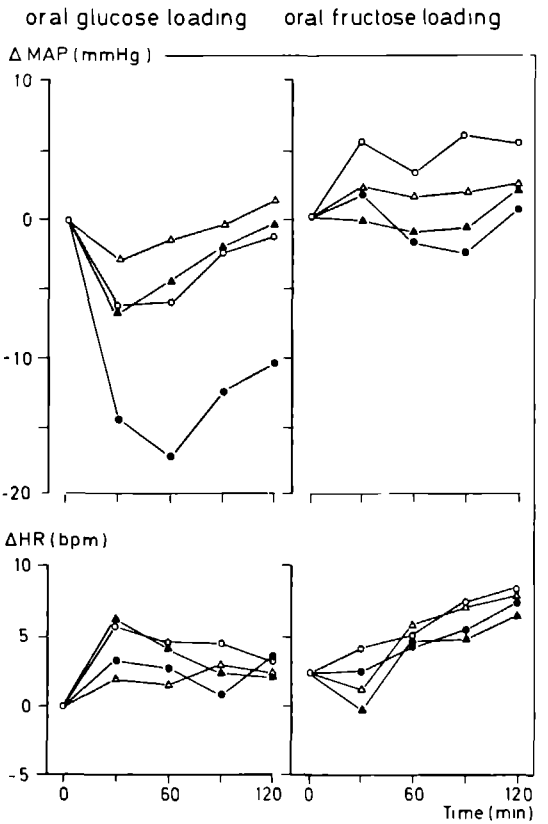

Figure 1 Mean changes of mean arterial pressure (MAP) and heart rate (HR) after oral glucose- (left) and oral fructose loading (right) in young normotensive (YN, open triangles) young hypertensive (YH, solid triangles), normotensive elderly (EN, circles) and hypertensive elderly subjects (EH, dots).
Curve analysis revealed significant differences for MAP after glucose between EH and EN ($p \leq 0.001$) and between EH and YH ($p \leq 0.001$), and for HR after glucose between EN and YN ($p \leq 0.05$).

Heart rate

The influence of glucose and fructose on heart rate was not significantly different in any group (Table 2 and 3). After both tests a slight increase in heart rate was observed. Remarkably, in view of the corresponding decrease in BP, a significant increase of heart rate after glucose loading occurred in the EN group, whereas no increase occurred in the EH group.

Norepinephrine

Basal plasma norepinephrine levels before the glucose and fructose tests were sig-

nificantly higher in the EN than in the YN group. In addition, basal plasma norepinephrine levels were significantly higher in the EH than in YH group. Glucose loading resulted in a significant increase in norepinephrine level, lasting for 120 min in the YN group, 60 min in the YH and EN groups and 30 min in the EH group. Fructose loading resulted in significant increases in norepinephrine levels in the normotensive but not in the hypertensive groups.
The effects of glucose and fructose on plasma norepinephrine level were not significantly different in any of the groups except in the YN group, which had signifi-

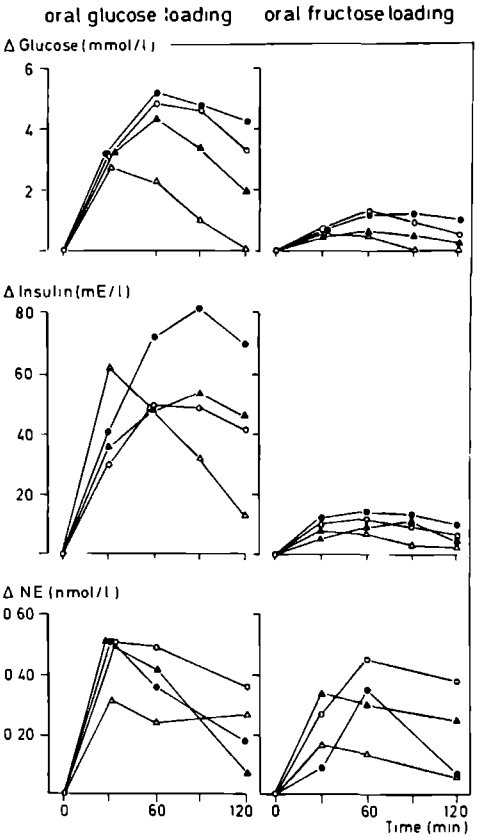

Figure 2 Mean changes of glucose, insulin and norepinephrine (NE) after oral glucose- (left) and oral fructose loading (right) in young normotensive (YN, open triangles), young hypertensive (YH, solid triangles), normotensive elderly (EN, circles) and hypertensive elderly subjects (EH, dots).
Curve analysis revealed significant differences for glucose after oral glucose between EN and YN ($p \leq 0.01$) and for glucose after fructose between EH and YH ($p \leq 0.01$) and between EN and YN ($p \leq 0.05$). Insulin and NE after fructose were significantly different between EN and YN ($p \leq 0.05$ and $p \leq 0.05$, respectively).

cantly higher norepinephrine levels after glucose than after fructose loading. Comparison of the curves of plasma norepinephrine responses after glucose did not yield any statistical significantly difference between the study groups (Fig 2).

Glucose and insulin

Oral fructose loading resulted in a slight but significant increase of plasma glucose and insulin not exceeding, however, an increase of plasma levels of > 1.3 mmol/l and 15 mU/l, respectively, in any of the groups (Fig 2). Maximum insulin responses were 62 mU/l at time 30 min in the YN group, 53 mU/l at time 90 min in the YH group, 50 mU/l at time 60 min in the EN group and 81 mU/l at time 90 min in the EH group. Comparison of the curves and area under the curves of insulin responses did not yield a significant difference between groups (Fig 2). The increase of plasma glucose after oral glucose loading was similar in the YH, EN and EH groups. In the YN group, however, the curve and the area under the curve of the increases of plasma glucose were significantly lower than in the EN group (Fig 2).

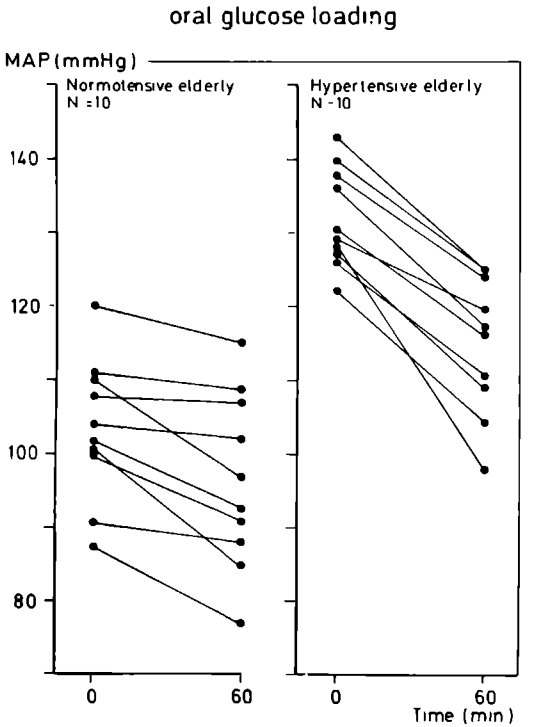

Figure 3 Individual changes in mean arterial pressure (MAP) after oral glucose loading in normotensive and hypertensive elderly persons.

Discussion

This study shows that BP decreases markedly after oral glucose loading in unselected elderly hypertensive patients without overt cardiovascular disease or diabetes mellitus and not taking antihypertensive medications. In addition, a slight but significant decrease in BP also was observed in healthy elderly normotensive and in young hypertensive subjects. In young normotensive subjects, however, BP did not change during this test. These findings indicate that the decrease in BP after oral glucose loading is an age- and BP-related phenomenon. In contrast, we did not observe an effect on BP in any of the study groups after oral ingestion of a fructose solution. Since fructose loading, contrary to isocaloric and isovolumic glucose loading, elicited only a small increase in plasma glucose and insulin levels, we suggest that glucose- and insulin-related factors play a specific role in the pathophysiology of the observed BP reductions.

The influence of oral glucose loading on BP in elderly subjects has not been studied extensively. Young et al [7] found no change in mean arterial pressure after administration of a 100 g of glucose solution to 12 elderly normotensive persons (mean age 72.9 $\pm$ 1.9 years). Robinson et al studied BP responses to glucose (50 g) ingestion in 5 orthostatic elderly and 5 elderly control subjects and found a marked decrease in BP in patients with orthostatic hypotension but not in control subjects [10].

An important role for carbohydrates and insulin in the postprandial BP reduction in elderly persons was first proposed by Lipsitz et al [1]. Based on earlier studies in their laboratory, they suggested that an age-related decrease of insulin-induced sympathetic nervous system activation may, at least in part, be responsible for postprandial hypotension. Failure of sympathetic nervous system activation was suggested to be mediated by blunting of baroreflex sensitivity by insulin or glucose, as was found in some studies [11,12]. We found that BP decrements were most pronounced in hypertensive elderly persons. Since baroreflex sensitivity decreases with BP and age [13,14,15], the substantial decrease in BP after glucose but not after fructose loading appears to support to their theory. However, the increases of plasma norepinephrine level and heart rate, both as a measure of sympathetic nervous system activation, were not significantly different after either type of test. BP in the group of elderly hypertensive patients decreased after glucose but not after fructose, in the face of a comparable activation of the sympathetic nervous system. Therefore, we suggest that insulin-mediated impairment of sympathetic nervous system activation does not play a major role in the decrease in BP after glucose.

Oral glucose and fructose loading may exert disparate effects on regional and systemic blood flow. Qamar et al [16], using a transcutaneous Doppler ultrasound method, found in healthy volunteers an increase of superior mesenteric blood flow of 53% at the end of the ingestion of an isotonic glucose solution. No significant change in blood flow was found after ingestion of a lactulose solution.

However, unlike fructose, very small amounts of lactulose are absorbed in normal subjects. Da Costa et al [17] studied patients with idiopathic autonomic failure and found a far greater decrease in BP after glucose than after xylose ingestion. Since in these patients neurocirculatory reflexes were absent, the findings suggest that the sugars had different effects on splanchnic blood pooling. Based on these studies we suggest that oral glucose loading induces a specific vasodilation of (splanchnic) vasculature, which, in elderly and hypertensive persons, is incompletely counterbalanced by activation of the sympathetic nervous system, due to an age- and BP related decrease of baroreflex sensitivity. Indeed, the maximal percent increases of norepinephrine levels after glucose loading in YN, YH, EN and EH were 40%, 37%, 30% and 22%, respectively. In addition, plasma levels of norepinephrine remained significantly elevated for 120, 90, 60 and 30 min, respectively.

Splanchnic or systemic vasodilation after glucose ingestion can be considered to be mediated by gut hormones. A possible role for vasoactive gastrointestinal peptides was recently suggested by Hoeldtke et al [18], who found that postprandial BP reductions in patients with autonomic neuropathy can effectively be abolished by subcutaneous administration of the somatostatin analogue SMS 201-995. However, attempts to identify such a hormone have been unsuccessful.

Acknowledgement

We gratefully acknowledge the assistance of Jack Willemsen, Laboratory of Experimental and Chemical Endocrinology of the University Hospital of Nijmegen, who performed the plasma norepinephrine determinations. Preparation of this manuscript by Anky Verweijen is greatly appreciated.

References

1. Lipsitz LA, Nyqvist RP, Wei JY, Rowe JW Postprandial reduction in blood pressure in the elderly. N Engl J Med 1983,309:81-83.
2. Westenend M, Lenders JWM, Thien Th. The course of blood pressure after a meal a difference between young and elderly subjects. J Hypertension 1985,3(suppl 3):S417-S419.
3. Lipsitz LA, Fullerton KJ Postprandial blood pressure reduction in healthy elderly. J Am Geriatric Soc 1986,34:267-270
4. Lipsitz LA, Pluchino FC, Wei JY, Minaker KL, Rowe JW. Cardiovascular and norepinephrine responses after meal consumption in elderly (older than 75 years) persons with postprandial hypotension and syncope. Am J Cardiol 1986,58:810-815
5. Minaker KL, Rowe JW, Young JB, Sparrow D, Pallotta JA, Landsberg L Effect of age on insulin stimulation of sympathetic nervous system activity in man. Metabolism 1982,31:1181-1184.
6. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta JA, Landsberg L . Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. Diabetes 1981;30:219-225.

7. Young JB, Rowe JW, Pallotta JA, Sparrow D, Landsberg I Enhanced plasma norepinephrine response to upright posture and oral glucose administration in elderly human subjects. Metabolism 1980;29:532-539.
8. Hoffmann JJML, Willemsen JJ, Lenders JWM, Benraad ThJ. Reduced imprecision of the radioenzymatic assay of plasma catecholamines by improving the stability of the internal standards. Clin Chim Acta 1986,156·221-226
9. Koziol JA, Maxwell DA, Fukushima M, Colmerauer MEM, Pilch YH. A distribution-free test for tumor-growth curve analysis with application to an animal tumor immunotherapy experiment. Biometrics 1981;37:383-390.
10. Robinson BJ, Johnson RH, Lambie BG, Palmer KT. Autonomic responses to glucose ingestion in elderly subjects with orthostatic hypotension. Age and Ageing 1985;14:168-173.
11. Page MMcB, Watkins PJ. Provocation of postural hypotension by insulin in diabetic autonomic neuropathy. Diabetes 1976,25.90-95.
12. Appenzeller O, Goss JE Glucose and baroreceptor function: effects of oral administration of glucose on baroreceptor function in cerebrovascular disease and in other disorders with baroreceptor reflex block. Arch Neurol 1970;23:137-146.
13 Gribbin B, Pickering TG, Sleight P, Reto R. Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 1971,29:424 431.
14. Shimada K, Kitazumi T, Ogura H, Sadakane N, Ozawa T. Differences in age-independent effects of blood pressure on baroreflex sensitivity between normal and hypertensive subjects. Clin Sci 1986;70:489-494.
15. McGarry K, Laher M, Fitzgerald D, Horgan J, O'Brien F, O'Malley K. Baroreflex function in elderly hypertensives. Hypertension 1983; 5.763-766.
16. Qamar MI, Read AF, Mountford R Increased superior mesenteric artery blood flow after glucose but not lactulose ingestion. Q J of Med 1986;233.893-896
17. Da Costa DF, McIntosh C, Bannister R, Christensen NJ, Mathias CJ. Unmasking of the cardiovascular effects of carbohydrate in subjects with sympathetic denervation J Hypertension 1985;3(suppl 3).S447-S448.
18. Hoeldtke RD, O'Dorisio ThM, Boden G Treatment of autonomic neuropathy with a somatostatin analogue SMS-201-995. Lancet 1986, II:602-605.

CHAPTER IV

Oral versus intravenous glucose loading and its relation to postprandial blood pressure reduction in the elderly

R.W.M.M. Jansen and W.H.L. Hoefnagels.

Department of Geriatric Medicine, University Hospital Nijmegen, University of Nijmegen, Nijmegen, The Netherlands.

Parts of this paper have been published in:
J Hypertension 1987;5(suppl 5):S501-S503.
Br Med J 1987;295:671-672 (Letter).

CHAPTER IV

Oral versus intravenous glucose loading and its relation to postprandial blood pressure reduction in the elderly

Abstract

Blood pressure (BP) in the elderly may decrease after a meal or after oral glucose loading. A role for insulin in this hypotensive effect is suggested by our earlier finding that BP in elderly subjects remained unchanged after oral fructose loading. To determine whether the hypotensive effects of glucose loading is specifically mediated by gastrointestinal factors or vasodilator properties of insulin, we studied the effects of oral and intravenous glucose loading on BP, heart rate and plasma norepinephrine in normotensive and hypertensive elderly volunteers over 70 years of age. After oral glucose mean arterial BP fell by 16 ± 2 mm Hg ($p \leq 0.001$) in hypertensive elderly and by 8 ±1 mm Hg ($p \leq 0.001$) in normotensive elderly subjects. In contrast, we did not observe any effect of intravenous glucose loading on BP in either of the elderly groups. These data indicate that it is unlikely that a vasodilator effect of insulin plays an important role in the fall in BP after oral glucose. Therefore, we suggest that interference of insulin with a by age or disease diminished sympathetic response to the by oral glucose induced splanchnic vasodilation, may be responsible for the fall in BP in the elderly.

Introduction

Up to now there have been several studies which have shown that blood pressure (BP) may fall after a meal in the elderly and in patients with autonomic failure [1,2,3]. Although the clinical significance remains uncertain, Lipsitz et al have described eight institutionalized elderly patients with meal-related syncope and large postprandial BP declines [4]. In a recent study we found a similar reduction of BP in the elderly after an oral glucose loading [5]. Oral fructose loading, however, had no effect on BP in the elderly [5]. In addition, in patients with autonomic failure, there was a marked and prolonged fall in BP after oral glucose with only a small fall after oral xylose [6].

The mechanism of postprandial BP reduction is unknown, but is has been suggested that oral glucose induces a specific vasodilation of splanchnic vasculature, possibly mediated by stimulation of vasoactive gastrointestinal hormones or insulin,

which is incompletely counterbalanced by activation of the sympathetic nervous system [1,5]. Indeed, pretreatment with a somatostatin analogue octreotide (SMS 201-995), which inhibited the secretion of almost all gastrointestinal hormones [7], completely prevents the fall of BP after oral glucose [8]. On the other hand, octreotide may exert its beneficial effect by suppression of insulin secretion. These findings indicate that insulin might play an important role in the phenomenon of postprandial hypotension. Indeed, intravenous insulin has been reported to cause a decrease of BP and even hypotension and syncope in diabetic patients [9,10] and in patients with autonomic failure [11]. We therefore investigated the effects of oral glucose and intravenous glucose loading in healthy elderly volunteers. As postprandial BP reduction is related to baseline BP [1,5], both normotensive and hypertensive elderly persons were studied.

Methods

Ten hypertensive and 10 normotensive subjects, aged 70 years or older, were recruited by a newspaper announcement. Hypertension was defined as a supine systolic BP ≥160 mm Hg or a supine diastolic BP ≥95 mm Hg, measured after 20 min of rest using a standard sphygmomanometer. Antihypertensive drugs were withdrawn for at least one month before the study. All subjects were without a history of myocardial infarction, cerebrovascular accident, congestive heart failure or diabetes mellitus. The study was approved by the local ethical committee. The clinical characteristics of both groups are listed in Table 1. The two groups did not differ in age, Quetelet index or heart rate, only in BP.

Both oral glucose and intravenous glucose loading were performed in each subject with an interval of one week. All studies were carried out in the morning after an

Table 1 Clinical characteristics of subjects (mean ± SD)

		Normotensives (n=10)	Hypertensives (n=10)
Age (years)	mean	75± 4	74±5
	range	71–83	70–84
Sex (men/women)		5/ 5	4/ 6
Quetelet's-index (Kg/m^2)		24± 3	26± 3
Systolic BP (mm Hg)		149±13	189±17
Diastolic BP (mm Hg)		81± 7	102± 5*
Heart rate (beats/min)		62±10	70±14

*$p \leq 0.001$ when compared with normotensive subjects

BP = blood pressure

overnight fast. At time 0 min the subjects received 75 gram glucose in 300 ml of water orally or 40 gram glucose 40% solution/1.73 m^2 body surface area intravenously. BP was measured in the supine position using an Arteriosonde® and heart rate was calculated from an ECG-recording. BP and heart rate were measured at regular intervals of 5 min from −20 to 120 min. Five BP− and heart rate measurements, taken from time −20 to 0 min, were averaged and considered as the baseline BP and heart rate and further denoted as time 0 min. As the subjects consumed the glucose solution within 5 min, no measurement of BP and heart rate was performed at time 5 min after oral glucose. The glucose solution, which was given intravenously, was injected within 2 minutes. A 21 gauge butterfly needle was inserted 30 min before the start of the test in an antecubital vein and kept patent with physiologic saline. At time 0, 15, 30, 60 and 120 min blood samples were collected for measurement of glucose, insulin and plasma catecholamines [12].
Statistical comparisons between paired and unpaired observations were made with Student t test when appropriate; otherwise Wilcoxon's signed rank and ranked sum tests were used. To reduce the overall probability of a type I error, a level of significance of $p \leq 0.01$ (two-sided) was employed. Comparisons between curves were made with a distributionfree analysis of variance [13]. In this test a p-level of 0.05 or less was considered to be statistically significant. Mean arterial pressure (MAP) was calculated as the sum of diastolic BP and one third of pulse pressure. All values given in tables and text are expressed as mean ± sem, unless indicated otherwise.

Results

In Table 2 all baseline hemodynamic and biochemical data of both groups are listed. Fig 1 and 2 present the course of BP and heart rate after oral and intravenous glucose loading in the normotensive and hypertensive groups.

Table 2 Baseline values in both groups (mean ± sem).

	Normotensives		Hypertensives	
	oral	intravenous	oral	intravenous
Systolic BP (mm Hg)	137 ± 4	135 ± 5	175 ± 5	166 ± 5
Diastolic BP (mm Hg)	79 ± 2	78 ± 2	101 ± 2	96 ± 2
Heart rate (bpm)	62 ± 3	65 ± 2	70 ± 5	68 ± 4
Glucose (mmol/l)	4.9 ± 0.2	5.0 ± 0.2	4.9 ± 0.3	4.7 ± 0.2
Insulin (mU/l)	9 ± 1	9 ± 1	9 ± 1	10 ± 1
Norepinephrine (nmol/l)	1.78 ± 0.28	1.64 ± 0.13	1.66 ± 0.15	1.99 ± 0.25
Epinephrine (nmol/l)	0.16 ± 0.03	0.19 ± 0.03	0.19 ± 0.03	0.20 ± 0.05

BP = blood pressure.

After oral glucose systolic BP decreased in the normotensive subjects with a maximum of 6 ± 3 mm Hg (5%, p=0.01) and diastolic BP fell by 8 ± 1 mm Hg (11%, p≤0.001). MAP decreased from 98 ± 3 to 91 ± 3 mm Hg (8%, p≤0.001). In the hypertensive subjects systolic BP decreased significantly within 30 min reaching a maximum of 19 ± 4 mm Hg (11%, p≤0.01) at time 60 min. A similar pattern was found for the course of diastolic BP with a maximum decrease of 16 ± 2 mm Hg (15%, p≤0.001). MAP fell from 125 ± 2 to 109 ± 3 mm Hg (13%, p≤0.001). The decrease of MAP after oral glucose was significantly greater in the hypertensive group than in the normotensive group (curve analysis p=0.02). Five min after the start of the intravenous glucose injection, systolic BP decreased by 15 ± 3 mm Hg (11%, p≤0.01) in the normotensive group and by 13 ± 4 mm Hg (8%, p≤0.01) in

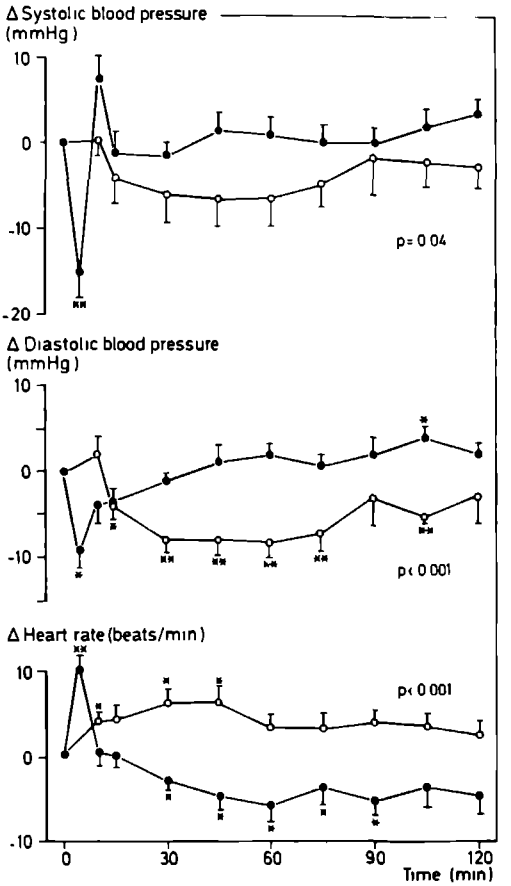

*Figure 1 Mean values of blood pressure and heart rate after oral (circles) and intravenous (dots) glucose loading in normotensive elderly subjects. * denotes p≤0.01 and ** p≤0.001 when compared with baseline values. The p-values given in the figure represent curve analysis between both types of test.*

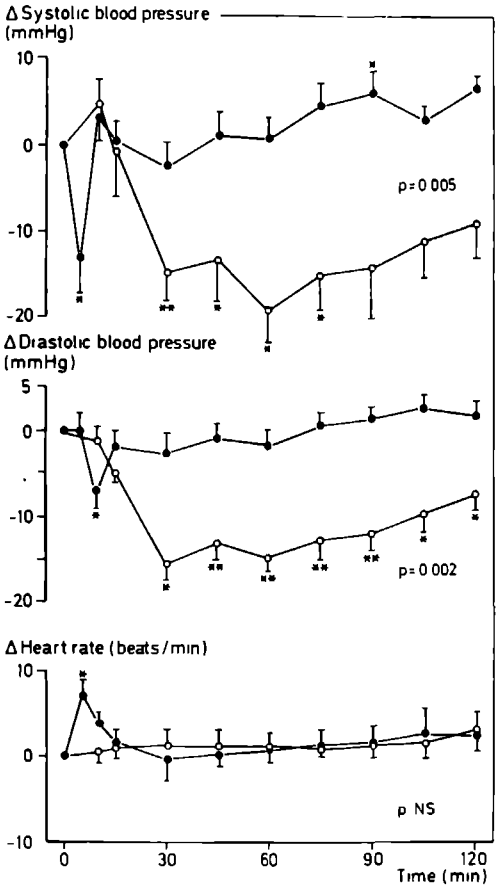

*Figure 2 Mean values of blood pressure and heart rate after oral (circles) and intravenous (dots) glucose loading in the hypertensive elderly subjects. * denotes $p \leq 0.01$ and ** $p \leq 0.001$ when compared with baseline values. The p-values given in the figure represent curve analysis between both types of test.*

the hypertensive subjects. Diastolic BP fell only in the normotensive group by 9 ± 3 mm Hg (11%, $p \leq 0.01$). Within 10 min after the start of injection systolic and diastolic BP had returned to baseline values and remained essentially unchanged in both groups. The p values for the comparison of the curves obtained with oral and intravenous glucose loading are given in Fig 1 and 2.

In the normotensive group, the heart rate increased from 62 ± 3 to 68 ± 3 beats/min (11%, $p \leq 0.01$) at time 30 min after oral glucose and decreased from 65 ± 2 to 59 ± 3 beats/min (9%, $p \leq 0.01$) at time 60 min after intravenous glucose loading (Fig 1). This difference in the heart rate response after both tests in the normotensives was highly significant ($p \leq 0.001$). The influence of oral and intravenous glucose loading on the heart rate was not significantly different in the hypertensive

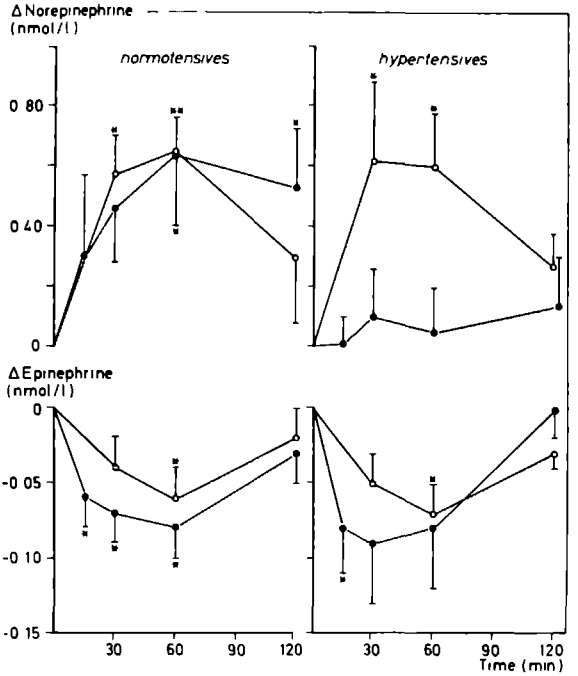

*Figure 3 Mean values of plasma norepinephrine and plasma epinephrine after oral (circles) and intravenous (dots) glucose loading in normotensive and hypertensive elderly subjects. * denotes $p \leq 0.01$ and ** $p \leq 0.001$ when compared with baseline values.*

group. Except for the values found at time 5 min no change in heart rate was observed after both tests.

Baseline plasma norepinephrine levels were not significantly different between the groups (Table 2). Plasma norepinephrine increased significantly in both groups after oral glucose (Fig 3). After intravenous glucose a similar response was found in the normotensive group, while in the hypertensives no change in plasma norepinephrine was found. However, this difference between both groups was not significant. The different response of plasma norepinephrine after both tests in the hypertensive elderly group almost reached the level of significance ($p=0.06$). Plasma epinephrine levels decreased in both groups after the two tests without any difference between groups and between tests (Fig 3).

Intravenous glucose loading resulted in a rapid increase of plasma glucose and plasma insulin with an observed maximum at time 15 min and a sluggish decrease thereafter (Fig 4). After oral glucose the maximum levels of plasma glucose and plasma insulin were reached at time 60 min. No difference between the groups was found in the plasma glucose and plasma insulin response after both types of tests. Analysis of the insulin curves showed a significant difference in either group between both tests.

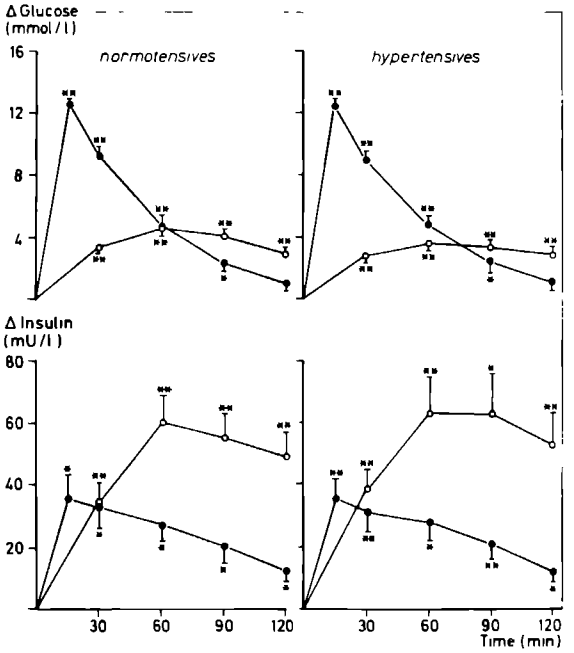

*Figure 4 Mean values of plasma glucose and plasma insuline after oral (circles) and intravenous (dots) glucose loading in normotensive and hypertensive elderly subjects. * denotes $p \leq 0.01$ and ** $p \leq 0.001$ when compared with baseline values.*

Discussion

This study demonstrates that in normo- and hypertensive elderly subjects, oral glucose loading lowered BP substantially within 30 min after the intake of the glucose solution. The magnitude of the reduction in MAP was almost twice as high in hypertensive as in elderly normotensives. In contrast, rapid intravenous injection of glucose led to an almost immediate fall of BP which returned to baseline values within 10 min after the start of the glucose injection and remained unchanged for the following two hours of observation.

The immediate fall of BP after administration of glucose 40% iv can be explained by the well-known vasodilating effect of rapidly and intravenously administered hypertonic solutions. All subjects experienced a flush and transient warm sensations. This hypotensive effect of hypertonic solutions (but probably also radiographic contrast media) should be borne in mind when these are administered to elderly and patients with autonomic failure [10].

Insulin may have vasodilator effects. In patients with chronic autonomic failure and in diabetic patients, intravenous insulin administration caused a decrease of BP [11,14]. Several studies demonstrated that insulin infusions in conscious dogs

resulted in a vasodilator effect of skeletal muscle vasculature [15,16]. In addition, intra-arterial infusions of insulin in the forearm of healthy young volunteers, caused an increase in forearm blood flow and a decrease in forearm vascular resistance. This vasodilator effect of insulin can be inhibited by pretreatment with propranolol, which suggests a beta adrenergic mechanism [17]. In the present study it is unlikely that a direct vasodilator effect of insulin plays an important role in the fall in BP after oral glucose, since we did not observe any effect of intravenous glucose administration on BP. Although the maximum insulin levels after oral glucose were higher than after intravenous glucose, this difference cannot account for the difference in BP response, since insulin levels at time 30 min, when a significant drop of BP occurred after oral but not after intravenous glucose loading, were not significantly different in either type of test.

The effects of both types of loading tests on sympathetic nervous system activity can be derived from changes in plasma norepinephrine. The clearance of plasma norepinephrine has been reported to increase or to remain unchanged after increments in endogenous insulin release and, therefore, cannot explain the increase of plasma norepinephrine concentrations [18]. Furthermore, it is unlikely that the rise in plasma norepinephrine is derived from an enhanced secretion by the adrenal medulla, because plasma epinephrine decreased. The increase of plasma norepinephrine after oral glucose loading may therefore reflect an activation of the sympathetic nervous system, elicited by the fall in BP. Indeed, when in the hypertensive elderly subjects glucose was given intravenously, no change in BP and plasma norepinephrine was found. In the normotensive elderly, however, plasma norepinephrine showed a similar increase after intravenous and oral glucose loading. This increase of plasma norepinephrine after intravenous glucose, in the absence of an effect on BP, might reflect an insulin-mediated stimulation of sympathetic nervous system activity, as was found in young volunteers [18], in diabetic patients without neuropathy [19] and in dogs [15]. The diverging effects of intravenous glucose loading on plasma norepinephrine responses between both elderly groups are difficult to explain, unless we consider a relative impairment of insulin-mediated activation of the sympathetic nervous system in hypertensive elderly patients, as was found in diabetic patients with autonomic neuropathy [19]. Finally, non-specific stimuli from the gastro-intestinal tract may contribute to the degree of sympathetic nervous system activation. Both oral fructose [5] and oral xylose loading [20] lead to an increase of plasma norepinephrine, without a concomitant rise of plasma insulin. On the other hand, preliminary data of our laboratory have shown that an isovolumic water loading does not induce an increase in plasma norepinephrine in hypertensive elderly subjects.

In the light of a possible role for insulin in postprandial BP reduction, a stimulative effect of insulin on the sympathetic nervous system and a vasodilating action of insulin are difficult to reconcile, unless interaction of insulin and norepinephrine could be demonstrated. Indeed, in several studies, insulin was found to impair the peripheral action of norepinephrine [21,22], and to facilitate the take-up of norepinephrine at the nerve terminals [23].

In conclusion, the mechanism of postprandial BP reduction is still unknown. Based on the findings that BP only falls after a meal or oral glucose loading, but not after oral fructose or intravenous glucose loading, we suggest that interference of insulin with a by age or disease diminished sympathetic response to splanchnic vasodilation, may be responsible for postprandial BP reduction in the elderly.

Acknowledgement

We wish to express our gratitude to J. Willemsen, Laboratory of Experimental and Chemical Endocrinology of the University Hospital of Nijmegen, who performed the plasma norepinephrine determinations

References

1 Lipsitz LA, Nyqvist RP, Wei JY, Rowe JW Postprandial reduction in blood pressure in the elderly N Engl J Med 1983,309 81-83

2 Jansen RWMM, Lenders JWM, Thien T, Hoefnagels WHL Antihypertensive treatment and postprandial blood pressure reduction in the elderly Gerontology 1987,95 363 368

3 Robertson D, Wade D, Robertson RM Postprandial alterations in cardiovascular hemodynamics in autonomic dysfunctional states Am J Cardiol 1981,48 1048-1052

4 Lipsitz LA, Pluchino FC, Wei JY, Minaker KL, Rowe JW Cardiovascular and norepinephrine responses after meal consumption in elderly (older than 75 years) persons with postprandial hypotension and syncope Am J Cardiol 1986,58 810-815

5 Jansen RWMM, Penterman BJM, van Lier HJJ, Hoefnagels WHL Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin Am J Cardiol 1987,60 1087 1091

6 Da Costa DF, McIntosh C, Bannister R, Christensen NJ, Mathias CJ Unmasking of the cardiovascular effects of carbohydrate in subjects with sympathetic denervation J Hypertension, 3(suppl 3), S447-S448

7 Williams G, Fuessl H, Kraenzlin M, Bloom SR Postprandial effects of SMS 201-995 on gut hormones and glucose tolerance Scand J Gastroenterol 1986,21(suppl 119) 73 83

8 Jansen RWMM, Lenders JWM, Peeters TL, van Lier HJJ, Hoefnagels WHL SMS 201-995 prevents postprandial blood pressure reduction in normotensive and hypertensive elderly subjects J Hypertension 1988,6 (suppl 4) S669-S672

9 Miles DW, Hayter CJ The effect of intravenous insulin on the circulatory responses to tilting in normal and diabetic subjects with special reference to baroceptor reflex block and atypical hypoglycaemic reactions Clin Sci 1968,34 419 430

10 Page MMcB, Watkins PJ Provocation of postural hypotension by insulin in diabetic autonomic neuropathy Diabetes 1976,25 90-95

11 Mathias CJ, da Costa DF, Fosbracy P, Christensen NJ, Bannister R Hypotensive and sedative effects of insulin in autonomic failure Br Med J 1987,295 161-163

12 Hoffmann JJMI, Willemsen JJ, Lenders JWM, Benraad ThJ Reduced imprecision of the radioenzymatic assay of plasma catecholamines by improving the stability of the internal standard Clin Chim Acta 1986,156 221-226

13 Koziol JA, Maxwell DA, Fukushima M, Colmerauer MFM, Pilch YH A distribution-free test for tumor growth curve analysis with application to an animal tumor immunotherapy experiment Biometrics 1981,37 383-390

14. Takata S, Yamamoto M, Yagı S, Nata Y, Ikeda T, Hattorı N. Peripheral circulatory effects of insulin in diabetes Angiology 1985;36:110-116.
15. Liang C-S, Doherty JU, Fallace R, Maekawa K, Arnold S, Gavras H, Hood WB. Insulin infusions in conscious dogs. Effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines. J Clin Invest 1982;69:1321-1336.
16. Reikeras O, Gunnes P. Effects of high doses of insulin on regional blood flows during acute left ventricular failure in dogs. European Heart J 1986;7:992-998.
17. Creager MA, Liang CS, Coffman JD Beta adrenergic-mediated vasodilator response to insulin in the human forearm. J Pharmacol Exp Ther 1985;235:709-714
18. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallota JA, Landsberg L. Fffect of insulin and glucose infusions on sympathetic nervous system activity in normal man. Diabetes 1981;30:219-225.
19. Yagı S, Takata S, Yamamoto M, Iwase N, Maeno K, Igarashi A, Noto Y, Ikeda T, Hattorı N. Effects of insulin on systemic and peripheral circulation and plasma noradrenaline. Jpn Circ J 1985; 49:894.
20. Tse TF, Clutter WE, Shah SD, Miller JP, Cryer PE. Neuroendocrine responses to glucose ingestion in man. Specificity, temporal relationships, and quantitative aspects. J Clin Invest 1983;72:270-277.
21. Lee JC, Downing SE. Effects of insulin on cardiac muscle contraction and responsiveness to norepinephrine Am J Physiol 1976;230:1360-1365.
22. Yagı S, Takata S, Kiyokawa H, Yamamoto M, Noto Y, Ikeda T, Hattorı N. Effects of insulin on vasoconstrictive responses to norepinephrine and angiotensin II in rabbit femoral artery and vein. Diabetes 1988;37:1064-1067
23. Bhagat B, Burke WJ, Dhalla NS Insulin-induced enhancement of uptake of noradrenaline in atrial strips. Br J Pharmacol 1981;74: 325-332.

CHAPTER V

The influence of oral glucose loading on baroreflex function in the elderly

René W.M.M. Jansen, MD and Willibrord H.L. Hoefnagels, MD.

Department of Geriatric Medicine, University Hospital Nijmegen, Nijmegen, The Netherlands.

Submitted for publication.

CHAPTER V

The influence of oral glucose loading on baroreflex function in the elderly

Abstract

Blood pressure (BP) in the elderly may decrease after a meal or after oral glucose loading. It has been suggested that eating may affect BP homeostasis through an insulin-induced blunting of baroreflex sensitivity. We investigated the effects of oral glucose loading on baroreflex sensitivity in young normotensives and in elderly normo- and hypertensive subjects. BP was measured by a new non-invasive device, Finapres, which measures BP continuously in the finger. In both elderly groups mean arterial pressure fell significantly after the glucose load (by 11 ± 1 mm Hg, $p \leq 0.001$ in the hypertensives and by 8 ± 2 mm Hg, $p \leq 0.01$ in the normotensive subjects), whereas no change in BP was found in the young group. Baroreflex sensitivity was lower in both elderly groups than in young normotensives. Glucose loading had no influence on baroreflex sensitivity in the three groups. Therefore, we concluded that other factors are involved in the phenomenon of postprandial BP reduction in the elderly.

Introduction

It has been known for several years that blood pressure (BP) in the elderly may fall after a meal [1,2]. This phenomenon is related to BP level and age [1,2]. A similar reduction of BP can be found after oral glucose loading [3], but not after oral fructose [3] or intravenous glucose loading [4]. The fall in BP after oral glucose starts about 15 min after ingestion and reaches its maximum within about 60 min [4]. The decrease in BP after oral glucose can completely be prevented by pretreatment with the somatostatine analogue octreotide (SMS 201-995) [5]. These effects of octreotide are possibly mediated by suppression of insulin secretion. Therefore we consider that insulin might play an important role in the phenomenon of postprandial hypotension. Lipsitz et al suggested that eating may affect BP homeostasis in the elderly through insulin-induced blunting of baroreflex sensitivity [1]. This suggestion was based on the findings of Appenzeller et al who found that oral glucose decreased baroreceptor response to Valsalva maneuver in young and old patients with cerebrovascular diseases or peripheral neuropathy [6].
The present study was designed to investigate whether a decrease of baroreflex function after oral glucose loading may contribute to the postprandial fall of BP in the elderly.

Methods

For this study three groups of subjects, recruited by a newspaper announcement, were studied: elderly hypertensives (EH), elderly normotensives (EN) and young normotensives (YN). All persons were healthy and no participant had a history of myocardial infarction, congestive heart failure, cerebrovascular accident, diabetes mellitus, chronic respiratory disease or mental deterioration. None of the elderly had a history of falls. All elderly subjects were 70 years or older. All EH had uncomplicated essential hypertension and had not taken antihypertensive medication for at least two weeks before the study. The clinical characteristics of the three groups are listed in Table 1. The two elderly groups did not differ in age, Quetelet's index or heart rate but did so in BP. The study was approved by the local ethical committee and all subjects gave written informed consent.

Table 1 Clinical characteristics (mean ± SD) of Young Normotensives (YN), Elderly Normotensives (EN) and Elderly Hypertensives (EH).

	YN (n=10)	EN (n=15)	EH (n=15)
Sex (men/women)	5 / 5	6 / 9	7 / 8
Age (years) mean	26± 4	76± 4	73± 3
range	21–32	71–84	70–80
Quetelet index (kg/m^2)	21± 2	26± 3	28± 3
Systolic BP (mm Hg)	115± 7	141± 12	185±18
Diastolic BP (mm Hg)	67± 6	79± 9	97± 9
Heart rate (beats/min)	61± 6	62± 8	66±10

* $p \leq 0.01$ versus young normotensives.
$p \leq 0.01$ versus elderly normotensives.
BP = blood pressure.

All studies were carried out in the morning after an overnight fast. In each subject an oral glucose loading test was performed. Glucose was given in a dose of 75 gram in 300 ml of water. At time 0 min the subjects consumed the glucose solution within 5 min. A 21 gauge butterfly needle was inserted 30 min before the start of the test in an antecubital vein and kept patent with physiologic saline. During the study the subjects stayed in the supine position. Before and 60 min after glucose ingestion blood samples were collected for determination of glucose, insulin and plasma catecholamine levels [7], and BP and heart rate were measured continuously during 5 min using the Finapres method. All BP and heart rate values were averaged and considered as the mean BP and heart rate. The Finapres (TNO-

Finapres, model 5, The Netherlands) uses the volume clamp method of Penaz and is a fully automated instrument that allows a continuous non-invasive measurement of finger arterial pressure. The details of this method have been described elsewhere [8,9].

Baroreflex sensitivity was estimated both with the phenylephrine and nitroglycerin method [10], by graded intravenous bolus injections, beginning with a dose of 50 μg and increasing the dose with 50 μg until a change in systolic BP of about 20 mm Hg was obtained or a maximum of 150 μg was reached. Systolic pressures for each beat and corresponding RR interval were recorded with a personal computer and the slope of the linear regression line was calculated. In each subject three injections of both drugs were given before and 60 min after glucose injection. The average of the three slopes of the regression lines was considered to represent the baroreflex sensitivity.

Statistical comparisons between paired and unpaired observations were made with Student's t-test when appropriate, otherwise Wilcoxon's signed rank and ranked sum tests were used. A p-level of 0.05 (two-sided) or less was considered to be of statistical significance. Correlation coefficients were calculated according to Pearson or to the non-parametric Spearman's rank correlation test. All values given in tables and text are expressed as mean ± standard error of the mean, unless indicated otherwise.

Results

In Table 2 all baseline hemodynamic and biochemical data of the three groups are listed. The mean changes of systolic BP, diastolic BP, mean arterial pressure and heart rate at 60 min after the glucose loading are presented in Fig 1. In both elderly

Table 2 Baseline values in the three groups (mean ± sem).

	YN	EN	EH
Systolic BP (mm Hg)	125 ± 4	135 ± 5	181 ± 4
Diastolic BP (mm Hg)	64 ± 2	64 ± 2	84 ± 3
Mean arterial pressure (mm Hg)	81 ± 3	87 ± 3	107 ± 5
Heart rate (beats/min)	61 ± 2	62 ± 2	66 ± 3
Glucose (mmol/l)	4.1 ± 0.1	4.9 ± 0.2§	5.0 ± 0.2
Insulin (mU/l)	6 ± 1	8 ± 1	10 ± 2
Norepinephrine (nmol/l)	0.95 ± 0.15	1.66 ± 0.14§	1.68 ± 0.30
Epinephrine (nmol/l)	0.13 ± 0.02	0.13 ± 0.02	0.13 ± 0.02

§ $p \leq 0.01$ versus young normotensives.
$p \leq 0.001$ versus elderly normotensives.
BP = blood pressure.

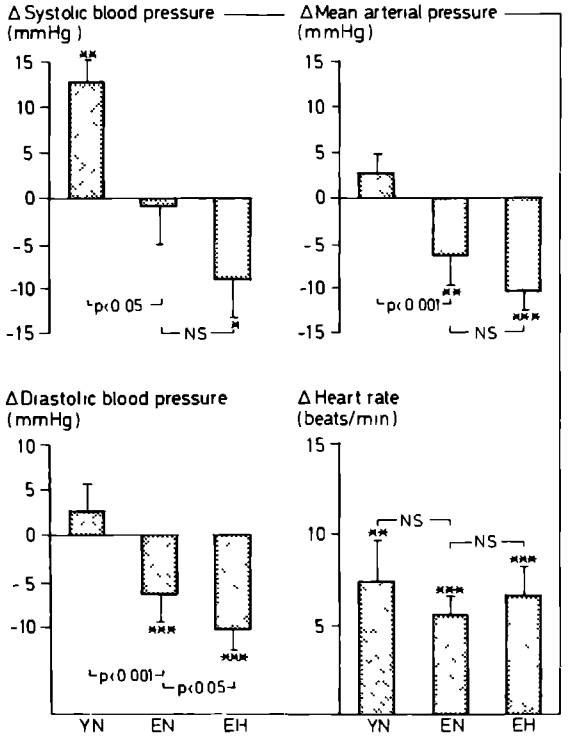

Figure 1 Mean changes of blood pressure and heart rate one hour after oral glucose loading in young normotensives (YN), elderly normotensives (EN), and elderly hypertensive subjects (EH).
** denotes $p \leq 0.05$, ** $p \leq 0.01$ and *** $p \leq 0.001$ when compared with baseline values.*

groups mean arterial pressure fell significantly after the glucose loading whereas in the YN mean arterial pressure remained essentially unchanged. In none of the subjects the fall of BP caused any subjective symptoms. In all three groups an increase of heart rate was observed, without statistically significant differences between groups.

The results of baroreflex sensitivity are shown in Table 3. Baroreflex sensitivity, as established by both methods, in the normo- and hypertensive elderly groups were significantly less than that of the YN. Furthermore, the values in the EH were lower than that of EN. Glucose loading has no significant influence on baroreflex sensitivity in the three groups, nor with the phenylephrine method nor with the nitroglycerin method. When the change in mean arterial pressure was correlated with baroreflex sensitivity, a weak but significant correlation was found; $r=0.50$, $p \leq 0.01$ for the phenylephrine method and $r=0.49$, $p \leq 0.01$ for the nitroglycerin method.

Table 3 Values of baroreflex sensitivity (ms/mm Hg) before and after oral glucose loading.

	Phenylephrine		Nitroglycerin	
	before	after	before	after
Young Normotensives	30.4 ± 2 7	30.2 ± 3.2	14.9 ± 2.2	13.1 ± 1 6
Elderly Normotensives	8 0 ± 0 9§§	9.4 ± 0.9	6.3 ± 0 9§	5.9 ± 1.2
Elderly Hypertensives	5.8 ± 0.9	5.1 ± 0.7	3.1 ± 0.4	2.8 ± 0.4

§ p≤0 01 and §§ p≤0.001 versus young normotensives
p≤0 01 versus elderly normotensives

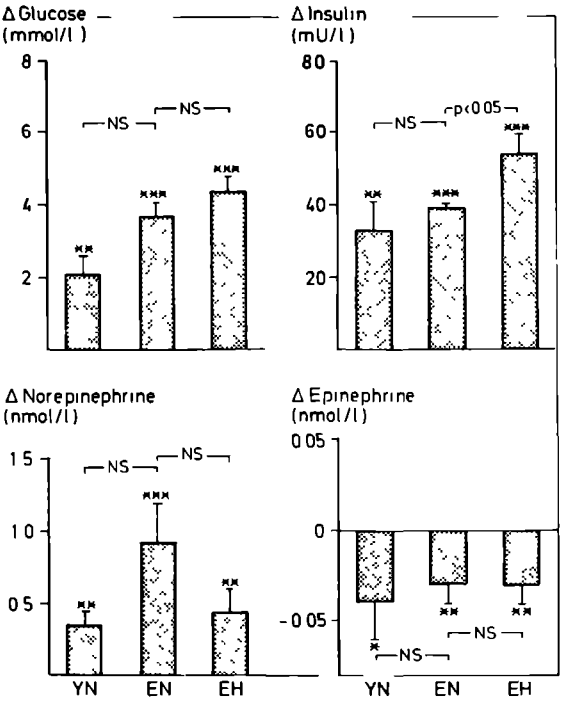

*Figure 2 Mean changes of glucose, insulin, norepinephrine and epinephrine one hour after oral glucose loading in young normotensives (YN), elderly normotensives (EN), and elderly hypertensive subjects (EH). * denotes p≤0.05, ** p≤0.01 and *** p≤0.001 when compared with baseline values.*

Oral glucose administration resulted in an increase of plasma glucose concentration (Fig 2). Baseline glucose levels were higher in the elderly groups than in YN. There was no difference between the groups in the increase of plasma glucose. In all groups plasma insulin levels rose significantly after the glucose load. The increase of plasma insulin was higher in EH when compared with EN. There was no correlation between the increase in plasma insulin and the decrease in mean arterial pressure.

Baseline plasma norepinephrine levels were significantly higher in both elderly groups than in the YN group, whereas no difference could be found between EN and EH. Glucose loading resulted in an increase in norepinephrine level of 37 ± 10% ($p \leq 0.01$) in YN, 55 ± 14% ($p \leq 0.001$) in EN and 29 ± 7% ($p \leq 10.01$) in EH. The percentual or absolute changes of plasma norepinephrine between the groups were not significantly different. In all groups plasma epinephrine levels decreased significantly after oral glucose without any difference between the groups.

Discussion

An important role for carbohydrates and insulin in the postprandial BP reduction in the elderly was first proposed by Lipsitz et al [1]. Apparently the hypotensive effects of carbohydrates are especially related to oral glucose, since we previously found that BP decreases after oral glucose loading but not after oral fructose loading [3]. Using the Finapres device, the present study confirms the BP-related decrease in BP after an oral glucose load in the elderly. A slight and insignificant increase of mean arterial pressure was found in young normotensives.

The Finapres provides a BP device with the possibility to measure BP and heart rate continuously and noninvasively. The BP values measured with this method are slightly lower than intra-arterial recordings [8,9]. However, this device follows intra-arterial patterns faithfully. It was therefore concluded that because of the inherent risks of intra-arterial BP monitoring, the Finapres can replace most intraarterial pressure recordings [8]. The recently developed method of estimating baroreflex sensitivity by means of spectral analysis creates the possibility of a completely non-invasive measurement of baroreflex sensitivity [11].

Since baroreflex sensitivity decreases with BP and age [12,13,14], a further decrease of baroreflex function in response to glucose and/or insulin could theoretically be responsible for an insufficient activation of the sympathetic nervous system. In elderly subjects, a by oral glucose induced vasodilation of splanchnic vasculature and an impairment of sympathetic nervous system activation may result in a fall in BP. However, this study clearly shows that baroreflex function, as established by the phenylephrine and nitroglycerin method, was not affected by oral glucose loading. In contrast to our results, Appenzeller et al found that oral glucose decreased baroreceptor responses in patients with cerebrovascular disease or diseases affecting baroreceptor function [6]. In their study baroreceptor

function was assessed during the release phase of valsalva maneuver. Additional support for a decreased sensitivity of baroreceptor function by insulin was also derived from some other studies [15,16]. Miles et al have shown that after intravenous insulin in normal and diabetic subjects, head-up tilting resulted in a greater fall in mean arterial pressure than during tilting without insulin [15]. Similar results were found by Page et al who studied patients with diabetes and autonomic neuropathy [16]. From these experiments it was suggested that insulin administration might impair baroreflex mechanisms [1].

The values of baroreflex sensitivity as established by the nitroglycerin method were lower than found by using phenylephrine. This difference is probably due to different aspects of baroreflex function which are measured. In addition, it has been demonstrated that the correlation among both measurement techniques is very low [10].

Although we did not find any effect of oral glucose loading on baroreceptor function, an influence of insulin at another level of the sympathetic nervous system cannot be excluded. Firstly, insulin has a direct stimulatory effect on the sympathetic nervous system, even in the absence of hypoglycemia [17]. On the other hand, administration of insulin to patients with autonomic failure causes a decrease of BP [18]. These contrasting findings are difficult to reconcile, unless interaction of insulin and norepinephrine, at the level of the norepinephrine receptors, could be demonstrated. Indeed, in several studies, insulin has been found to impair the peripheral action of norepinephrine [19,20], and to facilitate the take-up of norepinephrine at the nerve terminals [21]. Secondly, insulin may have vasodilator effects. It has been demonstrated that insulin infusions in conscious dogs resulted in a vasodilator effect of skeletal muscle vasculature [22,23]. In addition, intra-arterial infusions of insulin in the forearm of healthy young volunteers, causes an increase in forearm blood flow and a decrease in forearm vascular resistance. This vasodilator effect of insulin can be inhibited by pretreatment with propranolol, which suggests a beta adrenergic mechanism [24]. On the bases of these studies we suggest that the fall in BP in the elderly after oral glucose or after meals is caused by a shift of blood volume to the splanchnic vasculature which is incompletely counterbalanced by activation of the sympathetic nervous system, and secondly that glucose related factors, such as insulin, may interfere with a normal sympathetic nervous system activation or may have direct vasodilator properties. However it is unlikely that a vasodilator effect of insulin primarily determines the fall in BP after oral glucose [4].

The basal concentration of plasma norepinephrine was higher in the elderly subjects. It is generally agreed that norepinephrine increases with age [25,26], but it remains to be determined whether this is due to a reduced clearance of norepinephrine [27] or to an increased rate of neuronal release [28]. Despite a greater fall in BP to oral glucose loading, the lower increase of plasma norepinephrine in the hypertensive elderly is in accordance with the age and BP related decrease of baroreflex sensitivity as found in this study and other studies [12,13,14].

In conclusion, our data indicate that in the elderly BP decreases after oral glucose. Baroreflex sensitivity is diminished in the elderly, but oral glucose loading did not further decrease baroreflex sensitivity. Therefore, other factors such as interference of insulin with a normal function of the sympathetic nervous system or vasodilator effects of insulin might be responsible for the fall in BP after meals or oral glucose.

Acknowledgement

The authors wish to express their gratitude to J. Willemsen, Laboratory of Experimental and Chemical Endocrinology of the University Hospital of Nijmegen, who performed the plasma norepinephrine determinations and to L. Sewuster, Department of Medical Information Processing, for writing the computer programs.

References

1. Lipsitz LA, Nyqvist RP, Wei JY, Rowe JW. Postprandial reduction in blood pressure in the elderly. N Engl J Med 1983;309:81-83.
2. Jansen RWMM, Lenders JWM, Thien T, Hoefnagels WHL. Antihypertensive treatment and postprandial blood pressure reduction in the elderly. Gerontology 1987;95:363-368.
3. Jansen RWMM, Penterman BJM, van Lier HJJ, Hoefnagels WHL. Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin Am J Cardiol 1987,60:1087-1091.
4. Jansen RWMM, Hoefnagels WHL. Influence of oral and intravenous glucose loading on blood pressure in normotensive and hypertensive elderly subjects. J Hypertension 1987;5(suppl 5): S501-S503.
5. Jansen RWMM, Lenders JWM, Peeters TL, van Lier HJJ, Hoefnagels WHL. SMS 201-995 prevents postprandial blood pressure reduction in normotensive and hypertensive elderly subjects. J Hypertension 1988;6 (suppl 4).S669-S5672
6. Appenzeller O, Goss JE. Glucose and baroreceptor function: effects of oral administration of glucose on baroreceptor function in cerebrovascular disease and in other disorders with baroreceptor reflex block. Arch Neurol 1970;23:137-146.
7. Hoffmann JJML, Willemsen JJ, Lenders JWM, Benraad ThJ. Reduced imprecision of the radioenzymatic assay of plasma catecholamines by improving the stability of the internal standard. Clin Chim Acta 1986;156:221-226
8. Imholz BPM, van Montfrans GA, Settels JJ, van der Hoeven GMA, Karemaker JM, Wieling W. Continuous non-invasive blood pressure monitoring: Reliability of Finapres device during the valsalva manoeuvre. Cardiovasc Res 1988;22:390-397
9. Molhoek GP, Wesseling KH, Settels JJ, van Vollenhoven E, Weeda HWA, de Wit B, Arntzenius AC. Evaluation of the Penàz servoplethysmo-manometer for the continuous, non-invasive measurement of finger blood pressure. Basic Res Cardiol 1984;79:598-609.
10. Goldstein DS, Horwitz D, Keiser HR. Comparison of Techniques for measuring baroreflex sensitivity in man. Circulation 1982;66:432-439.
11. Robbe HWJ, Mulder LJM, Ruddel H, Langewitz WA, Veldman JBP, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. Hypertension 1987;10:538-543.

12 Gribbin B, Pickering TG, Sleight P, Peto R Effect of age and high blood pressure on baroreflex sensitivity in man Circ Res 1971,29 424-431
13 Shimada K, Kitazumi T, Ogura H, Sadakane N, Ozawa T Differences in age-dependent effects of blood pressure on baroreflex sensitivity between normal and hypertensive subjects Clin Sci 1986,70 489 494
14 McGarry K, Laher M, Fitzgerald D, Horgan J, O'Brien F, O'Malley K Baroreflex function in elderly hypertensives Hypertension 1983,5 763-766
15 Miles DW, Hayter CJ The effect of intravenous insulin on the circulatory responses to tilting in normal and diabetic subjects with special reference to baroceptor reflex block and atypical hypoglycaemic reactions Clin Sci 1968,34 419-430
16 Page MMcB, Watkins PJ Provocation of postural hypotension by insulin in diabetic autonomic neuropathy Diabetes 1976,25 90-95
17 Rowe JW, Young JB, Minaker KL, Stevens AL, Pallota JA, Landsberg L Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man Diabetes 1981,30 219-225
18 Mathias CJ, da Costa DF, Fosbraey P, Christensen NJ, Bannister R Hypotensive and sedative effects of insulin in autonomic failure Br Med J 1987,295 161 163
19 Lee JC, Downing SF Effects of insulin on cardiac muscle contraction and responsiveness to norepinephrine Am J Physiol 1976,230 1360 1365
20 Yagi S, Takata S, Kiyokawa H, Yamamoto M, Noto Y, Ikeda T, Hattori N Effects of insulin on vasoconstrictive responses to norepinephrine and angiotensin II in rabbit femoral artery and vein Diabetes 1988,37 1064 1067
21 Bhagat B, Burke WJ, Dhalla NS Insulin-induced enhancement of uptake of noradrenaline in atrial strips Br J Pharmacol 1981,74 325 332
22 Liang C S, Doherty JU, Faillace R, Mackawa K, Arnold S, Gavras H, Hood WB Insulin infusions in conscious dogs Effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines J Clin Invest 1982,69 1321 1336
23 Reikeras O, Gunnes P Effects of high doses of insulin on regional blood flows during acute left ventricular failure in dogs European Heart J 1986,7 992-998
24 Creager MA, Liang CS, Coffman JD Beta adrenergic-mediated vasodilator response to insulin in the human forearm J Pharmacol Exp Ther 1985,235 709-714
25 Esler MD, Hasking GJ, Willet IR Leonard PW, Jennings GL Noradrenaline release and sympathetic nervous system activity J Hypertension 1985,3 117 129
26 Floras J, Jones JV, Hassan O, Osikowska BA, Sever PS, Sleight P Failure of plasma norepinephrine to consistently reflect sympathetic activity in humans Hypertension 1986,8 641-649
27 Esler M, Skews H, Jackman I G, Bobik A, Korner P Age-dependence of noradrenaline kinetics in normal subjects Clin Sci 1981,60 217-219
28 Rubin PC, Scott PJW, McLean K, Reid JI Noradrenaline release and clearance in relation to age and blood pressure in man Eur J Clin Invest 1982,12 121-125

CHAPTER VI

The effect of oral glucose, protein, fat and water loading on blood pressure in hypertensive elderly subjects

R.W.M.M. Jansen[1], MD, T.L. Peeters[2], PhD, H.J.J. van Lier[3], MSc and W.H.L. Hoefnagels[1], MD.

[1]Department of Geriatric Medicine, University Hospital Nijmegen, [3]Department of Statistical Consultation, University of Nijmegen, Nijmegen, The Netherlands, and [2]Department of Medical Research, Gut Hormone Laboratory, University of Leuven, Leuven, Belgium.

Submitted for publication.

CHAPTER VI

The effect of oral glucose, protein, fat and water loading on blood pressure in hypertensive elderly subjects

Abstract

In elderly subjects blood pressure (BP) may fall after a meal. It can be reproduced by oral glucose, but the effect of fat and protein ingestion on postprandial BP is unknown. Furthermore, we hypothesized that vasoactive gastrointestinal hormones are involved in the etiology of postprandial BP reduction. In 10 hypertensive elderly subjects (mean age 74 ± 3 years), we studied the effects of oral glucose, fat, protein and water loading on BP in relation to plasma concentrations of vasoactive intestinal polypeptide (VIP), somatostatin and insulin. Glucose, fat (cream) and protein (Protein 88®) were given in a dose of 75 gram in 300 ml of water. Glucose loading resulted in a decrease of mean arterial pressure by 14 ± 2 mm Hg ($p \leq 0.001$). In contrast, the ingestion of fat, protein or water appeared to have no influence on BP. Somatostatin increased after fat and protein loading, whereas VIP only increased after fat loading. These data indicate that postprandial BP reduction in the elderly is related to glucose related factors, since BP did not decline after fat or protein ingestion. The gut hormone VIP does not seem to play a role in this phenomenon.

Introduction

It has been known for several years that blood pressure (BP) in the elderly may fall after a meal [1,2]. This phenomenon is related to baseline BP and age [2,3]. We have previously reported that in normo- and hypertensive elderly subjects a comparable reduction of BP can be found after oral glucose loading [3], but not after oral fructose [3] or intravenous glucose loading [4]. These findings may indicate that oral glucose loading induces a specific vasodilation of splanchnic vasculature, possibly mediated by stimulation of vasoactive gastrointestinal hormones. On the other hand, it has been suggested that insulin may play an important role in postprandial hypotension by interference with a normal function of the sympathetic nervous system [1,3]. Although the mechanism of postprandial BP reduction in the elderly and in patients with autonomic failure still remains to be elucidated, it seems to be clear that the aforementioned factors, in addition to a by age and BP

diminished baroreflex sensitivity, are involved in the phenomenon of postprandial BP reduction. However, it is also of interest to know whether protein, fat or water may interfere with postprandial BP homeostasis. The present study was designed to investigate the effects of different food components on BP in relation to plasma concentrations of vasoactive intestinal polypeptide (VIP), somatostatin and insulin in healthy hypertensive elderly subjects aged 70 years or older.

Methods

Ten hypertensive elderly subjects (4 men, 6 women), aged 70 years or older, were recruited by a newspaper announcement. Antihypertensive drugs had been withdrawn for at least two weeks before the study. None of the subjects had a history of myocardial infarction, cerebrovascular accident, congestive heart failure, or diabetes mellitus. The clinical characteristics of the study group were: age 74 ± 3 (SD) years (range 70 to 80 years), Quetelet index 26 ±3 (SD) kg/m^2, BP 170/93 ± 15/10 (SD) mm Hg and heart rate 69 ± 8 (SD) beats/minute. The study was approved by the local ethical committee and all subjects gave written informed consent.

In each subject an oral glucose, fat, protein and water load was performed in a random order, on separate occasions with an interval of at least 3 days. All test solutions were made up to 300 ml with water containing the same amount of nutrients (75 gram). Glucose was given in a dose of 75 g in 300 ml of water. For the protein solution we used 85 g of Protein 88® (Wander, Sandoz BV, The Netherlands) in 300 ml of water, containing 75 g whey protein, 1.7 g fat and 1.7 g lactose. Fat was given as 215 g cream in 300 ml of water. This solution contains 75 g fat, 4.3 g protein and 6 g carbohydrates. For the water loading 300 ml of water at room temperature was used.

All studies were carried out in the morning after an overnight fast. At time 0 min the subjects consumed the test solution within 5 min. During the study the patients remained in a semi-recumbent position. BP was measured by an automatic recorder (Arteriosonde 1225, Roche) and heart rate was calculated from an ECG-recording at 5 min intervals from −30 to 150 min. Three BP- and heart rate measurements, taken from time −10 to 0 min, were averaged and considered as the baseline BP and heart rate and further denoted as time 0 min. This value and the means of the 3 values around the 30, 60, 90, 120 and 150 min time points (i.e. 25, 30, 35 min) were used in the analyses. A 21 gauge butterfly needle was inserted in an antecubital vein 30 min before the test solutions were given and kept patent with 154 mmol/l NaCl. At time 0, 30, 60, 90, 120 and 150 min blood samples were collected for determination of glucose, insulin, triglycerides, VIP, somatostatin and plasma catecholamines. Plasma catecholamines were measured using a radioenzymatic assay [5]. Samples for determination of VIP and somatostatin were collected in EDTA tubes containing 0.5 ml aprotinin (Trasylol®). The sam-

ples were centrifuged immediately and the plasma stored at −20 °C until assay. VIP was measured by radioimmuno assay [6] using labeled VIP obtained from New England Nuclear (NEN, Dreiech, FRG), standard VIP and antibody obtained from UCB, Bioproducts (Braine L'Alleud, Belgium). The sensitivity of this assay was such that it could detect changes of 1.5 pmol/l with 95% confidence. Somatostatin was measured by radioimmuno assay [7] using labeled somatostatin, standard and antibody obtained from Amersham, Belgium. The sensitivity of this assay was such that it could detect changes of 0.3 pmol/l with 95% confidence. All samples were analyzed in duplicate at the same time in each assay.

Statistical comparisons between paired and unpaired observations were made with Student's t tests when appropriate; otherwise Wilcoxon's signed rank and ranked sum tests were used. To reduce the overall probability of a type I error, a level of significance of $p \leq 0.01$ (two-sided) was employed. The Kruskall-Wallis test was used to compare baseline values in the four tests. Comparisons between curves were made with a distribution-free analysis of variance [8]. Firstly, all curves were analyzed together. In this test a p value of 0.05 or less was considered to be statistical significant. When a difference was found, the curves after glucose, fat and protein loading were independently compared with the curves following water loading. To study the independent effects of glucose, insulin, VIP and somatostatin on BP responses one hour after the ingestion of the test solutions, a multiple regression analysis was performed within the groups. Mean arterial pressure (MAP) was calculated as the sum of diastolic BP and one third of pulse pressure. All values given in tables and text are expressed as mean ± standard error of the mean, unless indicated otherwise.

Results

In Table 1 all baseline hemodynamic, biochemical and hormonal data of the four tests are listed. No significant difference was found between the baseline values in the four test groups. Fig 1 presents the changes in BP and heart rate after the four loading tests.

After oral glucose systolic BP decreased significantly within 30 min and reached its maximum at time 60 min (15 ± 3 mm Hg, $p \leq 0.001$). A similar pattern was found for the change in diastolic BP with a maximum decrease of 13 ±2 mm Hg ($p \leq 0.001$). MAP fell from 111 ± 2 to 97 ± 2 mm Hg (13%, $p \leq 0.001$). After fat, protein and water loading BP remained essentially unchanged. The p values for the comparison of the BP-curves obtained with the four test solutions are given in Table 2. The change of MAP following oral glucose was significantly greater than the change of MAP after water loading.

After oral glucose, heart rate increased from 69 ± 3 to 74 ± 3 ($p \leq 0.01$) at time 30 min. Following fat, heart rate increased from 70 ± 4 to 75 ± 4 ($p \leq 0.01$) at time 60 min and to 77 ± 4 ($p \leq 0.01$) at time 150 min. Protein loading did not affect heart

Table 1 Baseline values before ingestion of the four test solutions

	Glucose	Fat	Protein	Water
MAP (mm Hg)	111 ± 2	108 ± 3	111 ± 4	110 ± 3
Heart rate (bpm)	69 ± 3	70 ± 4	70 ± 4	74 ± 4
Glucose (mmol/l)	4.9 ± 0.2	4.9 ± 0.2	5.0 ± 0.2	5.1 ± 0.2
Insulin (mU/l)	10 ± 2	10 ± 2	12 ± 2	13 ± 2
Triglycerides (mmol/l)	1.6 ± 0.3	1.3 ± 0.2	1.7 ± 0.3	1.5 ± 0.3
Norepinephrine (nmol/l)	1.73 ± 0.24	1.84 ± 0.31	1.65 ± 0.23	1.94 ± 0.38
Epinephrine (nmol/l)	0.14 ± 0.02	0.13 ± 0.03	0.15 ± 0.04	0.10 ± 0.02
VIP (pmol/l)	17 ± 2	14 ± 2	17 ± 2	17 ± 2
Somatostatin (pmol/l)	6 ± 1	6 ± 1	5 ± 1	6 ± 1

rate. After water a slight decrease of heart rate was observed. Comparison between the heart rate curves showed a significant difference between glucose versus water loading and fat versus water loading.

The course of the glucose and insulin values is depicted in Fig 2. Following oral glucose loading, plasma glucose concentration rose to a maximum of 9.3 ± 0.7 mmol/l ($p \leq 0.001$) at time 60 min. After fat and protein loading a slight but significant decrease was found, but water ingestion did not affect glucose levels. Oral glucose resulted in an increase of insulin levels, with a maximum at time 90 min. A smaller but also significant rise was observed 30 and 60 min after protein loading, and 30 min after fat. Water was again without effect. The curve of plasma insulin following oral glucose was significantly different from those after fat, protein and water loading.

Initially, fat loading induced a small decrease of plasma triglycerides but at time 90 min a significant increase of 0.3 ± 0.1 mmol/l ($p \leq 0.01$) was found. Maximum triglyceride levels (2.4 ± 0.3 mmol/l, $p \leq 0.001$) were reached at time 150 min. Oral glucose and protein loading both resulted in a decrease of plasma triglycerides whereas water loading did not have any effect.

The values of plasma catecholamines are shown in Fig 3. After both oral glucose and fat loading a significant increase in plasma norepinephrine of 37% and a significant decrease in plasma epinephrine was found. Protein and water loading had no influence on the plasma concentrations of norepinephrine and epinephrine. Comparison between the curves of norepinephrine showed that there was a difference between glucose versus water loading and fat versus water loading. There was no difference between the curves of epinephrine when analyzed together.

The data of somatostatin and VIP are given in Fig 4. Oral glucose and water loading did not result in a change of somatostatin and VIP levels. A marked increase of plasma somatostatin (192%) was found after fat and a smaller increase of 69%

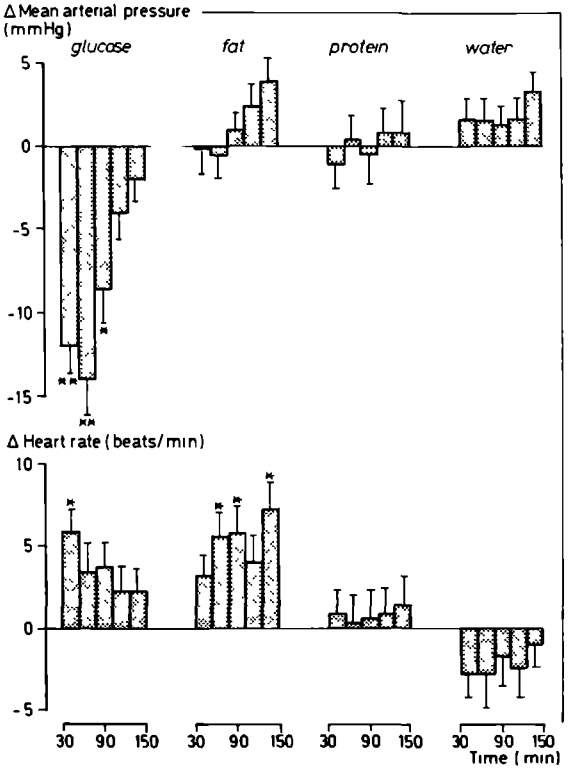

*Figure 1 Changes of mean arterial pressure and heart rate after ingestion of the four test solutions. * denotes p≤0.01 and ** p≤0.001 when compared with baseline values.*

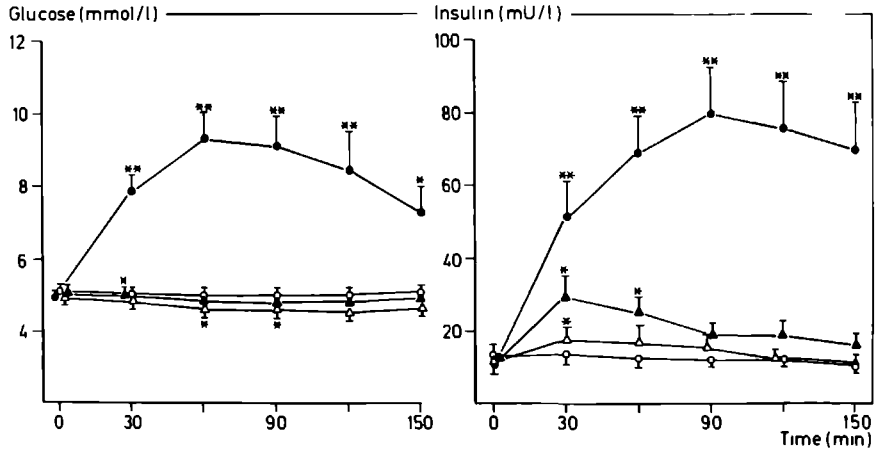

*Figure 2 Mean plasma glucose and insulin concentrations before and after glucose (dots), fat (open triangles), protein (solid triangles) and water (circles) loading. * denotes p≤0.01 and ** p≤0.001 when compared with baseline values.*

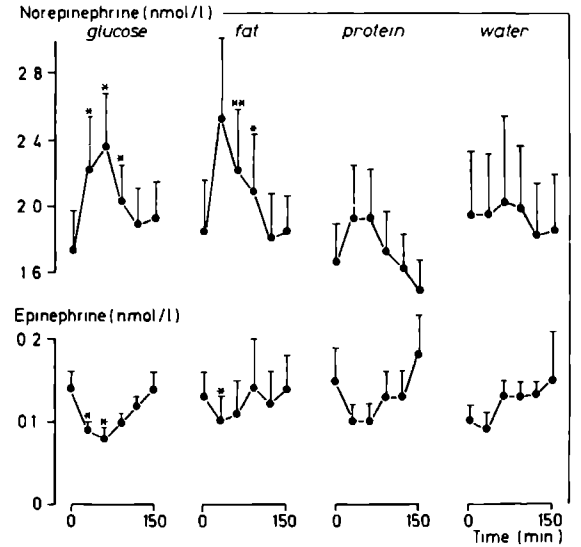

*Figure 3 Mean plasma norepinephrine and epinephrine concentrations before and after the four test solutions. * denotes p≤0.01 and ** p≤0.001 when compared with baseline values.*

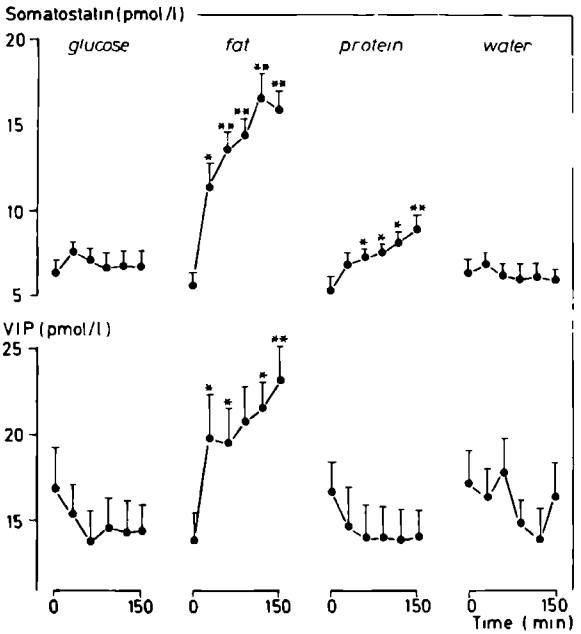

*Figure 4 Mean plasma somatostatin and vasoactive intestinal polypeptide (VIP) concentrations before and after the four test solutions. * denotes p≤0.01 and ** p≤0.001 when compared with baseline values.*

Table 2 P-values of analysis of variance between the different curves.

	All	Glucose vs Water	Fat vs Water	Protein vs Water
MAP	$p \leq 0.001$	$p \leq 0.001$	NS	NS
Heart rate	$p \leq 0\ 01$	$p \leq 0.05$	$p \leq 0.01$	NS
Glucose	$p \leq 0.001$	$p \leq 0.001$	NS	NS
Insulin	$p \leq 0.001$	$p \leq 0.001$	$p \leq 0.05$	$p \leq 0.01$
Triglycerides	$p \leq 0.001$	NS	$p \leq 0.01$	NS
Norepinephrine	$p \leq 0.05$	$p \leq 0.01$	$p \leq 0.05$	NS
Epinephrine	NS	–	–	–
VIP	$p \leq 0.001$	NS	$p \leq 0.01$	NS
Somatostatin	$p \leq 0.001$	NS	$p \leq 0.001$	$p \leq 0.01$

NS = not significant

after protein loading. The curves of somatostatin following fat and protein both differed from the curve after water loading. Only fat loading resulted in a significant increase of plasma VIP levels, differing significantly from the curve after water loading.
Regression analysis revealed that the change in glucose, insulin, VIP and somatostatin concentrations were not significantly correlated with the change of MAP.
All subjects completed the study without any problems. A few subjects volunteered a heavy feeling in the upper abdomen during the fat loading.

Discussion

The data in this study document that BP in healthy hypertensive elderly subjects falls following oral glucose, but not so, however, after oral fat, protein and water loading. This glucose induced fall in BP is comparable in magnitude to the decrease in BP as found in previous studies after meals [2] or oral glucose [3]. To our knowledge, the effects of different nutrients on BP have only been studied in patients with autonomic failure. Mathias et al recently reported that BP in patients with autonomic failure not only falls after oral glucose loading, but also after fat and protein loading [9]. Fat loading, compared to glucose, had a smaller, slower and less sustained effect, while protein loading had a small, transient hypotensive effect. Hoeldtke et al reported on an elderly patient with autonomic neuropathy who developed a drop in BP of 60 - 80 mm Hg after dextrose, fat (Lipomul) and protein (Propac) loading [10].
The different test solutions as used in the present study were isovolemic. They contained the same amount of nutrients, but differed in osmolality. It is unlikely,

however, that differences in osmolality accounted for the different effects on BP Firstly, we previously found that fructose, administered in an isosmotic solution, as compared to glucose, had no influence on BP [3] Secondly, it has been demonstrated that there are no changes in plasma electrolytes, osmolality and haematocrit after a meal in patients with autonomic failure This suggests that a shift of fluid into the gut or a contraction in plasma volume is unlikely to be responsible [11]

The results of the present study and of previous studies in which we found that BP only fell after oral glucose, but not after oral fructose [3] or intravenous glucose loading [4], suggest that oral glucose induces a specific vasodilation, possibly mediated by vasoactive gastrointestinal hormones Indeed, we found that pretreatment with a somatostatine analogue octreotide (SMS 201-995) prevents the fall of BP after oral glucose loading [12] In the present study we measured VIP, which is known to have vasoactive properties [13,14] It can be hypothesized that splanchnic or systemic vasodilation after oral glucose is mediated by this gut peptide, causing a shift of blood to the splanchnic area In the elderly this may lead to a fall in BP due to an insufficient activation of the sympathetic nervous system

VIP infusions in man produce a dose-dependent decrease of diastolic BP with an increase in heart rate [15] However, the physiologic role of VIP in splanchnic vasodilation is not clear and it has been suggested that VIP may play a role as a neurotransmitter but not as a circulating hormone [14] After intraduodenal instillation of fat a rise occurs in plasma VIP [16] However, VIP is not released in healthy young subjects after ingestion of a meal [17] or oral glucose [18] In the present study we found a significant response of VIP only after fat loading, howe ver, without a concomitant change of BP These data confirm our earlier report that oral glucose does not induce a rise in VIP in the elderly [12] and therefore, we conclude that VIP, as reflected in peripheral plasma concentrations, does not play an important role in postprandial BP reduction in the elderly

It has been demonstrated that in normal human subjects, infusion of somatostatin reduced splanchnic blood flow by 30% [19] Somatostatin has an inhibitory effect on virtually all gastrointestinal hormones [20] It can be argued that somatostatin plays a modulating role in splanchnic vasodilation by suppressing vasoactive gut peptides Indeed, our findings of an increase of somatostatin after fat and protein loading are in support of this theory, although apparently VIP is not involved

It has been shown that in young volunteers, ingestion of carbohydrate, fat and protein meals increased superior mesenteric artery blood flow to the same extent [21] Drinking water [21] or a lactulose solution [22] did not affect superior mesenteric artery blood flow, indicating that the chemical nature of nutrients and not the volume per se is a factor that determines postprandial mesenteric vasodilation Indeed, it became clear in dogs that postprandial intestinal hyperemia is related to the absorption and local oxidative metabolism [23] It still remains to be studied whether the nutrients fat, protein and carbohydrates cause different effects on splanchnic blood flow in the elderly

Other factors which may be responsible for the glucose-induced fall of BP in the elderly are a by age or disease diminished sympathetic response to splanchnic vasodilation, interference of insulin with a normal sympathetic nervous system function [24,25,26] and perhaps additional vasodilator effects of insulin.
In patients with chronic autonomic failure and in diabetic patients, intravenous insulin administration caused a decrease of BP [24,27,28]. Several studies demonstrated that insulin infusions resulted in a vasodilator effect in dogs and healthy man [29,30]. When oral glucose is given, the rise in plasma insulin, in addition to splanchnic vasodilation, might impose too great a burden on the homeostatic capacity of BP regulation. Against a role for insulin tells the absence in this study and previous studies [3,4,12] of a correlation between the increase of plasma insulin and the decrease in BP after oral glucose loading.
The effects of the loading tests on sympathetic nervous system activity can be derived from changes in plasma norepinephrine. Despite the fact that BP only fell after oral glucose, plasma norepinephrine increased not only after glucose but also after fat loading. The present results may indicate that the activation of the sympathetic nervous system following oral nutrients is not only a response to a fall in BP. Indeed, it has been shown that also xylose [31] and fructose loading [3] induce an increase in plasma norepinephrine, without changes in BP. Therefore, non-specific stimuli from the gastro-intestinal tract seem to contribute to the degree of sympathetic nervous system activation.
In conclusion our data indicate that in hypertensive elderly subjects BP decreases only after oral glucose, but not after fat, protein or water loading. The gut hormone VIP does not seem to be involved in the etiology of postprandial hypotension. Therefore we suggest that glucose-related factors may be responsible for the fall in BP in the elderly.

Acknowledgement

The authors wish to express our gratitude to J. Willemsen, Laboratory of Experimental and Chemical Endocrinology of the University Hospital of Nijmegen, who performed the plasma norepinephrine determinations and to R. Lamers for dietary assistance.

References

1. Lipsitz LA, Nyqvist RP, Wei JY, Rowe JW. Postprandial reduction in blood pressure in the elderly. N Engl J Med 1983;309:81-83.
2. Jansen RWMM, Lenders JWM, Thien T, Hoefnagels WHL. Antihypertensive treatment and postprandial blood pressure reduction in the elderly. Gerontology 1987;95:363-368.
3. Jansen RWMM, Penterman BJM, van Lier HJJ, Hoefnagels WHL. Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin. Am J Cardiol 1987;60:1087-1091.

4 Jansen RWMM, Hoefnagels WHL Influence of oral and intravenous glucose loading on blood pressure in normotensive and hypertensive elderly subjects. J Hypertension 1987,5(suppl 5):S501-S503
5. Hoffmann JJML, Willemsen JJ, Lenders JWM, Benraad ThJ Reduced imprecision of the radioenzymatic assay of plasma catecholamines by improving the stability of the internal standard. Clin Chim Acta 1986;156:221-226.
6. Noseda A, Peeters TL, Delhaye M, Bormans V, Couvreur Y, Vandermoten G, De Francquen P, Rocmans P, Yernault JC Increased plasma motilin concentrations in small cell carcinoma of the lung. Thorax 1987,42·784-789
7. Peeters TL, Depraetere Y, Vantrappen GR. Simple extraction method and radioimmunoassay for somatostatin in human plasma Clin Chem 1981,27:888-891.
8. Koziol JA, Maxwell DA, Fukushima M, Colmerauer MEM, Pilch YH. A distribution-free test for tumor-growth curve analysis with application to an animal tumor immunotherapy experiment Biometrics 1981;37.383-390.
9. Bannister R, da Costa DF, Forster S, Fosbraey P, Mathias CJ. Cardiovascular effects of lipid and protein meals in autonomic failure. J Physiol 1987;377:62P.
10. Hoeldtke RD, O'Dorisio TM, Boden G Prevention of postprandial hypotension with somatostatin. Ann Intern Med 1985;103:889-890.
11 Mathias C, da Costa D, Bannister R: Postcibal hypotension in autonomic disorders, in R Bannister (ed): Autonomic failure. A textbook of clinical disorders of the autonomic nervous system Oxford, Oxford University Press, 1988,367-380
12. Jansen RWMM, Peeters TL, Lenders JWM, van Lier HJJ, van 't Laar A, Hoefnagels WHL. Somatostatin analogue octreotide (SMS 201-995) prevents the decrease of blood pressure after oral glucose loading in the elderly. J Clin Endocrinol Metab 1989,68.752-756
13. Said SI. Vasoactive peptides Hypertension 1983,5·S17-S26.
14 Chou CC, Mangino MJ, Sawmiller DR: Gastrointestinal hormones and intestinal blood flow, in AP Shepherd and DN Granger (ed): Physiology of the intestinal circulation. New York, Raven Press, 1984,121-130.
15. Domschke S, Domschke W, Bloom SR, et al Vasoactive intestinal peptide in man: pharmacokinetics, metabolic and circulatory effects. Gut 1978;19:1049-1053.
16. Schaffalitzky de Muckadell OB, Fahrenkrug J, Holst JJ, Lauritzen KB. Release of vasoactive intestinal polypeptide (VIP) by intraduodenal stimuli. Scand J Gastroent 1977;12:793-799.
17. Mitchell SJ, Bloom SR Measurement of fasting and postprandial plasma VIP in man. Gut 1978;19:1043-1048.
18. Sagor GR, Bryant MG, Ghatei MA, Kirk RM, Bloom SR. Release of vasoactive intestinal peptide in the dumping syndrome. Br Med J 1981,282·507-510.
19. Wahren J, Felig P. Influence of somatostatin on carbohydrate disposal and absorption in diabetes mellitus. Lancet II; 1976: 1213-1216
20. Reichlin S. Somatostatin. N Engl J Med 1983;309:1556-1564.
21 Qamar MI, Read AF. Effects of ingestion of carbohydrate, fat, protein, and water on the mesenteric blood flow in man Scand J Gastroenterol 1988;23:26-30.
22. Qamar MI, Read AE, Mountford R Increased superior mesenteric artery blood flow after glucose but not lactulose ingestion. Q J Med 1986;233:893-896
23. Sit SP, Nyhof R, Gallavan R, Chou CC. Mechanisms of glucose-induced hyperemia in the jejunum. Proc Soc Exp Biol Med 1980,163: 273-277.
24 Mathias CJ, da Costa DF, Fosbraey P, Christensen NJ, Bannister R. Hypotensive and sedative effects of insulin in autonomic failure Br Med J 1987,295.161-163.
25. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallota JA, I andsberg L. Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. Diabetes 1981,30.219-225.

26 Yagi S, Takata S, Kiyokawa H, Yamamoto M, Noto Y, Ikeda T, Hattori N Effects of insulin on vasoconstrictive responses to norepinephrine and angiotensin II in rabbit femoral artery and vein Diabetes 1988,37 1064-1067
27 Brown RT, Polinsky RJ, Lee GK, Deeter JA Insulin induced hypotension and neurogenic orthostatic hypotension Neurology 1986,36·1402-1406
28 Takata S, Yamamoto M, Yagi S, Nata Y, Ikeda T, Hattori N Peripheral circulatory effects of insulin in diabetes Angiology 1985,36 110-116
29 Liang C-S, Doherty JU, Faillace R, Maekawa K, Arnold S, Gavras H, Hood WB Insulin infusions in conscious dogs Effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines J Clin Invest 1982,69 1321-1336
30 Creager MA, Liang CS, Coffman JD Beta adrenergic-mediated vasodilator response to insulin in the human forearm J Pharmacol Exp Ther 1985,235 709-714
31 Tse TF, Clutter WE, Shah SD, Miller JP, Cryer PE Neuroendocrine responses to glucose ingestion in man Specificity, temporal relationships, and quantitative aspects J Clin Invest 1983,72 270 277

CHAPTER VII

Somatostatin analogue octreotide (SMS 201-995) prevents the decrease of blood pressure after oral glucose loading in the elderly

René W.M.M. Jansen[1], Theo L. Peeters[2], Jacques W.M. Lenders[3], Henk J.J. van Lier[4], Albert van 't Laar[3], Willibrord H.L. Hoefnagels[1].

[1]Department of Geriatric Medicine and [3]Department of Medicine, Division of General Internal Medicine, University Hospital Nijmegen, [4]Department of Statistical Consultation, University of Nijmegen, Nijmegen, The Netherlands, and [2]Department of Medical Research, Gut Hormone Laboratory, University of Leuven, Leuven, Belgium.

J Clin Endocrinol Metab 1989;68:752-756.

CHAPTER VII

Somatostatin analogue octreotide (SMS 201-995) prevents the decrease of blood pressure after oral glucose loading in the elderly

Abstract

In elderly subjects blood pressure (BP) may fall after a meal. The mechanism of this phenomenon is unknown, but it has been suggested that it may be mediated by insulin and/or vasoactive gut hormones. We studied in normo- and hypertensive elderly subjects, the effects of the synthetic long-acting somatostatin analogue octreotide (SMS 201-995) on the BP reduction that follows oral glucose administration in subjects who are recumbent and on their postglucose plasma vasoactive intestinal polypeptide (VIP) and insulin concentrations. After placebo treatment, mean arterial pressure fell by 15 ± 1 mm Hg ($p \leq 0.001$) in the 10 hypertensive subjects and by 7 ± 2 mm Hg ($p \leq 0.01$) in the 10 normotensive subjects. In contrast, when 50 μg octreotide were given sc, BP did not change significantly in either group. Oral glucose did not induce a rise in plasma VIP after either octreotide or placebo administration. The postglucose rises in plasma glucose concentrations were similar after octreotide and placebo treatments in both groups. After placebo administration the postglucose plasma insulin levels increased from 79 to 519 pmol/l in the hypertensive subjects and from 63 to 464 pmol/l in the normotensive subjects, whereas after octreotide treatment plasma insulin increased only little in either group. These data indicate that treatment with octreotide holds promise for patients with symptomatic postprandial hypotension, and that VIP does not seem to play a role in this phenomenon.

Introduction

Blood pressure (BP) may fall in elderly subjects after a meal [1,2]. This phenomenon is related to BP level and age [1,2]. Although its clinical significance is uncertain, Lipsitz et al described eight institutionalized elderly patients with meal-related syncope and large postprandial BP declines [3]. In addition, patients with autonomic dysfunction may become hypotensive after a meal [4]. The mechanism of postprandial BP reduction is unknown, but an impaired sympathetic reflex reactivity to splanchnic vasodilation might be responsible for it [1,5]. In earlier studies we found that the BP of elderly persons decreased after oral glucose

loading [5], but not after intravenous glucose [6] or oral fructose loading [5]. These findings indicated that oral glucose specifically induces vasodilation of splanchnic vasculature, possibly mediated by stimulation of vasoactive gastrointestinal hormones. On the other hand, insulin may interfere with the normal function of the sympathetic nervous system [7,8,9]. Hoeldtke et al found that postprandial hypotension in patients with autonomic neuropathy was abolished by subcutaneous administration of the long-acting somatostatin analogue octreotide (SMS 201-995) [10]. Octreotide has been demonstrated to decrease not only the secretion of almost all gastrointestinal hormones [11], but also splanchnic blood flow [12]. This study was designed to investigate the effects of octreotide on BP after oral glucose administration in relation to plasma vasoactive intestinal polypeptide (VIP) and insulin concentrations in normo- and hypertensive elderly subjects.

Materials and methods

Experimental subjects

Ten hypertensive and 10 normotensive subjects, aged 70 years or older, were recruited by a newspaper announcement. Hypertension was defined as a supine systolic BP of more than 180 mm Hg or a supine diastolic BP of more then 95 mm Hg measured after 20 min of rest at three consecutive visits using a standard sphygmomanometer. Antihypertensive drugs were withdrawn for at least two weeks before the study. None of the subjects had a history of myocardial infarction, cerebrovascular accident, congestive heart failure, or diabetes mellitus. The study was approved by the local ethical committee, and all subjects gave written informed consent. The clinical characteristics of both groups are listed in Table 1. The two groups did not differ in age, Quetelet index (body weight divided by height^2), or heart rate, but only in BP.

Table 1 Clinical characteristics of study subjects

		Normotensive (n=10)	Hypertensive (n=10)
Age (years)	mean	74± 4	74± 4
	range	71–83	70–80
Sex (men/women)		4/ 6	3/ 7
Quetelet index (Kg/m^2)		27± 4	26± 3
Systolic BP (mm Hg)		135±11	183±16*
Diastolic BP (mm Hg)		78± 6	100± 6*
Heart rate (beats/min)		60± 9	63±12

* $p \leq 0.01$ when compared with normotensive subjects
BP = blood pressure
Mean ± SD

Pilot study

In a pilot experiment we studied the effect of 50 μg (1 ml) octreotide (in acetic acid) on BP and heart rate in 8 normotensive elderly subjects. After 30 min of rest in the supine position 1 ml octreotide or 1 ml placebo (154 mmol/l NaCl) was given sc in randomized single blind order. BP and heart rate were measured at 5 min intervals from −30 to 120 min. Mean arterial pressure (MAP) increased from 94 ± 3 (SE) to 103 ± 3 mm Hg ($p \leq 0.01$) after placebo treatment and from 98 ± 2 to 104 ± 2 mm Hg ($p \leq 0.01$) after octreotide. Calculation of the 95% confidence limits demonstrated no difference between the effects of placebo and octreotide. Heart rate did not change on either occasion.

Methods

Each subject received octreotide and placebo (154 mmol/l NaCl) followed by oral glucose in double blind randomized order with an interval of 1 week. All studies were carried out in the morning after an overnight fast. At time 0 min the subjects consumed 75 g glucose in 300 ml water within 5 min. Octreotide (50 μg) or placebo was given sc 30 min before the glucose (time −30 min). During the study the subjects stayed in the supine position. BP was measured by an automatic recorder (Arteriosonde 1225, Roche) and heart rate was calculated from an ECG-recording at 5 min intervals from −30 to 120 min. The 3 BP− and heart rate measurements at −10, −5 and 0 min, were averaged and considered as the basal BP and heart rate (time zero values). This value and the means of the 3 values around the 30, 60, 90 and 120 min time points (i.e. 25, 30, and 35 min) were used in the analyses. A 21-gauge butterfly needle was inserted in an antecubital vein and kept patent with 154 mmol/l NaCl. At time zero, 30, 60 and 120 min blood samples were collected for measurement of glucose, insulin and VIP. Plasma glucose was measured with an autoanalyzer using the glucose oxidase method and plasma insulin was measured in duplicate by RIA. The samples for determination of VIP were collected in EDTA tubes containing 0.5 ml aprotinin (Trasylol®). The blood samples were centrifuged immediately, and the plasma was stored at −20 °C until assay. VIP was measured by RIA [13] using labeled VIP obtained from New England Nuclear (NEN, Dreiech, FRG) and standard VIP and antibody obtained from UCB, Bioproducts (Braine L'Alleud, Belgium). The sensitivity of this assay was such that it could detect changes of 1.5 pmol/l with 95% confidence. All samples from an individual subject were analyzed in duplicate at the same time in each assay.

Statistics

Statistical comparisons between paired and unpaired observations were done by t test when appropriate; otherwise Wilcoxon's signed rank and ranked sum tests were used. To reduce the overall probability of a type I error, a level of significance of $p \leq 0.01$ was employed (Bonferroni's correction). The response curves were compared with a distribution-free analysis of variance [14]. In this test a p

level of 0.05 or less was considered to be statistically significant. To study the independent effects of insulin and VIP on BP responses multiple regression analysis was performed. MAP was calculated as the sum of diastolic BP and one third of pulse pressure. All values given in the tables and text are expressed as the mean ± SE, unless indicated otherwise.

Results

Blood pressure and Heart rate

Fig 1 and 2 shows the BP and heart rate measurements after placebo and octreotide administration in the hypertensive and normotensive groups. In both groups MAP fell significantly after glucose administration following previous placebo administration. The percentage MAP decline after oral glucose was significantly greater in the hypertensive than in the normotensive subjects ($p \leq 0.05$). In no subject did the fall in BP cause any subjective symptoms. In contrast, when octreotide was given before oral glucose, BP did not change in either group. In the hypertensive group there was a significant difference in systolic BP, diastolic BP, and

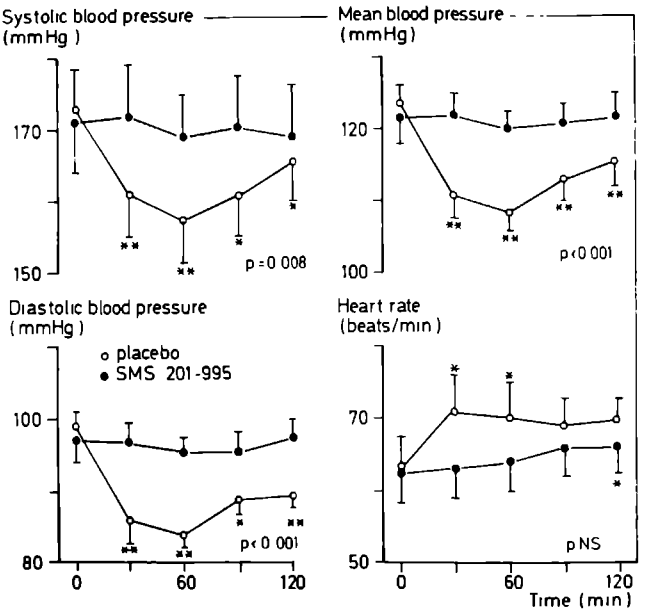

*Figure 1 Mean (± SE) blood pressure and heart rate after glucose ingestion following placebo or octreotide (SMS 201-995) administration in the hypertensive elderly subjects. The p-values shown represent the results of curve analysis between placebo and octreotide. * denotes $p \leq 0.01$ and ** $p \leq 0.001$ when compared with baseline values (Time 0).*

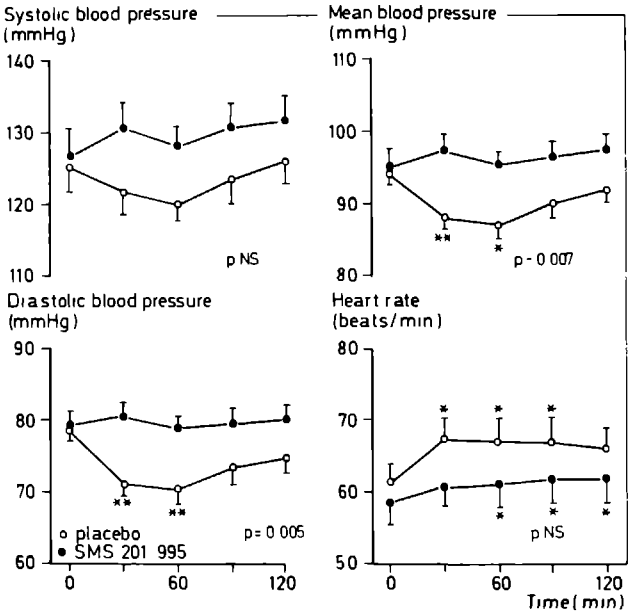

*Figure 2 Mean (± SE) blood pressure and heart rate after glucose ingestion following placebo or octreotide (SMS 201-995) administration in the normotensive elderly subjects. The p-values shown represent the results of curve analysis between placebo and octreotide. * denotes $p \leq 0.01$ and ** $p \leq 0.001$ when compared with baseline values (Time 0).*

MAP after octreotide administration compared to those after placebo. In the normotensive group there was a difference only in diastolic BP and MAP. There was no difference in baseline (Time zero) BP after octreotide or placebo treatment in either group.

In both groups heart rate increased significantly after placebo. After octreotide, there was a slight but significant increase in heart rate at the end of the study period in both groups. However, no significant difference was found in the course of heart rate between octreotide and placebo treatments in either group. The baseline heart rates were similar in the hypertensive group, whereas in the normotensive group the baseline heart rate after octreotide treatment was lower than that after placebo ($p \leq 0.05$).

Plasma Glucose and Insulin

The plasma glucose and insulin values are shown in Fig 3. The mean plasma glucose concentrations increased after oral glucose administration after octreotide and placebo treatments in both groups. Comparison of the glucose response curves revealed no significant differences between octreotide and placebo treatments in either group. However, the rise of glucose at 30 min was significantly

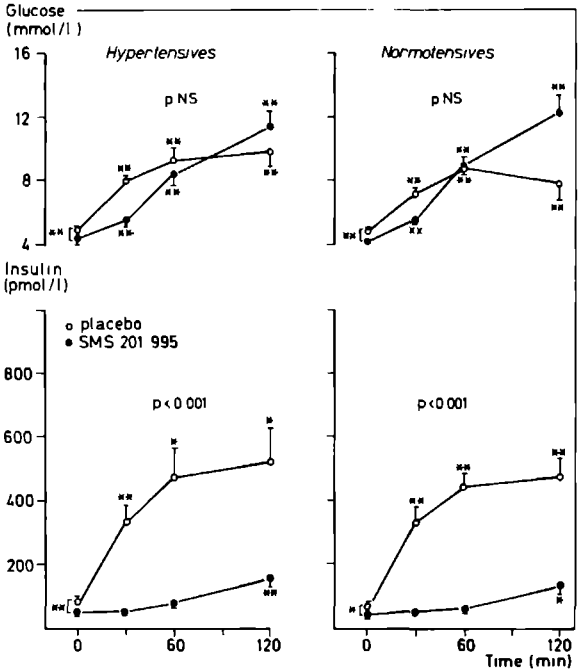

*Figure 3 Mean (± SE) plasma glucose and insulin concentrations after glucose ingestion following placebo or octreotide (SMS 201-995) administration in the normotensive and hypertensive elderly subjects. The p-values shown in the figure represent curve analysis between placebo and octreotide. * denotes $p \leq 0.01$ and ** $p \leq 0.001$ when compared with baseline values (Time 0) or between baseline values.*

lower after octreotide than after placebo in both groups. Baseline (Time zero) plasma glucose and insulin levels were significantly lower after octreotide than after placebo treatment in both groups. There was no difference in either group in the increase in insulin after oral glucose when placebo was given, but octreotide administration strongly inhibited the insulin response. Indeed, only at 120 min did plasma insulin increase slightly.

Plasma VIP

The plasma VIP values are shown in Table 2. Oral glucose did not result in a change in plasma VIP levels in the hypertensive group, but plasma VIP decreased slightly in the normotensive group. Octreotide administration did not change the basal plasma VIP levels or the VIP levels after oral glucose. Regression analysis revealed no correlations between the changes in plasma insulin or VIP concentrations and the reduction in MAP.

Table 2 Plasma VIP concentrations (pmol/l) after glucose ingestion following placebo and octreotide administration in normotensive and hypertensive elderly subjects.

	Normotensive		Hypertensive	
Time (min)	placebo	octreotide	placebo	octreotide
0	18 ± 1	16 ± 2	17 ± 2	18 ± 1
30	16 ± 2	19 ± 2	18 ± 2	17 ± 1
60	16 ± 1	18 ± 2	17 ± 2	17 ± 2
120	15 ± 1	16 ± 2	17 ± 1	17 ± 2

$p \leq 0.01$ when compared with basal values

Side effects

The sc injections of octreotide were uncomfortable because of the acetic acid solution. Some subjects had frequent defecation and slight abdominal pain during the afternoon and evening on the day of the study.

Discussion

Falls are an important cause of morbidity and even mortality in the elderly. Postprandial BP reduction may be of clinical importance, since Lipsitz et al recognized that syncope in the elderly is sometimes related to postprandial BP reductions [3]. Also, in patients with autonomical failure, large falls in BP after a meal have been reported [4,10]. Thus, postprandial BP decreases may precipitate dizziness, falls, or syncope. Because postprandial hypotension is related to basal BP [1,2], we studied both normotensive and hypertensive elderly subjects.

We found that a single 50 μg sc injection of the somatostatin analogue octreotide completely prevented the fall of BP after oral glucose in recumbent normotensive and hypertensive elderly subjects. This octreotide dose is known to markedly reduce plasma insulin and gut hormone concentrations [11]. In addition, we considered this dose as appropriate for the purpose of the study, since in a pilot study it had no effect on BP or heart rate in recumbent elderly subjects. Whether lower doses will be equally effective in preventing postprandial BP reduction in the elderly needs to be determined.

The mechanism by which octreotide exerted its beneficial effect on postprandial recumbent BP include suppression of insulin and/or vasoactive gastrointestinal hormone secretion and reduction in splanchnic blood flow.

Splanchnic or systemic vasodilation after oral glucose could be mediated by vasoactive gut hormones, such as VIP or neurotensin [15], causing a shift of blood

to the splanchnic area. In the elderly this could lead to a fall in BP, especially if there was insufficient activation of the sympathetic nervous system, due to an age and BP related decrease in baroreflex sensitivity [16,17].

VIP infusions in man produce a dose-dependent increase in heart rate and a decrease in diastolic BP [18]. In healthy young subjects, plasma VIP concentrations did not change significantly after ingestion of a meal [19] or oral glucose [20], and we found no postglucose change in plasma VIP levels in elderly subjects after either octreotide or placebo administration. Therefore, we conclude that VIP does not play an important role in the postprandial BP reduction. However, other vasoactive gut hormones, such as substance-P, neurotensin, or bradykinin, could be involved in the hypotensive effects of glucose administration.

The beneficial effect of octreotide on postprandial BP reduction could be due to a direct effect on splanchnic hemodynamics. Meals or oral glucose may increase superior mesenteric arterial blood flow [21,22]. Infusion of somatostatin or octreotide decreases splanchnic blood flow, possibly by a direct action on vascular smooth muscle [12,23,24]

The effects of octreotide on carbohydrate metabolism are apparent from the plasma glucose and insulin concentration curves. Somatostatin may be an inhibitory modulator of nutrient absorption [25], and impaired glucose absorption has been reported during somatostatin infusions [24]. We found that plasma glucose rose more slowly after octreotide, while the increased glucose levels at the end of the study period were probably due to the suppression of insulin release However, the glycemia did not seem to have an important effect on BP, since at 60 min, when the BP fall was maximal, the mean plasma glucose levels did not differ significantly from those after placebo treatment in the two groups.

Plasma insulin concentrations were significantly lower after octreotide administration, as also found in other studies [11] Intravenous insulin administration has been reported to cause a decrease in BP as well as hypotension and syncope in diabetic patients and patients with autonomic failure [9,26,27]. Furthermore, our earlier finding that BP in the elderly decreased after oral glucose, but not after oral fructose [5] suggested that insulin plays a role in postprandial blood pressure reduction Octreotide may, therefore, exert its beneficial effect by inhibiting insulin secretion

Several subjects reported abdominal discomfort after the study, and similar side-effects were reported in another study [11]. Perhaps these side-effects are related to the marked effect that somatostatin has on gut motility [28], which was recently also found for octreotide [29]

In conclusion, our data indicate that 50 μg octreotide, given sc before oral glucose administration, completely prevent the glucoseinduced decrease in BP in normo- and hypertensive elderly subjects. Thus, treatment with octreotide holds promise for patients with symptomatic postprandial hypotension VIP does not seem to play a role in the etiology of postprandial hypotension in the elderly The beneficial effects of octreotide may be due to a direct effect on the splanchnic circula-

tion, effects on the secretion of other vasoactive gut hormones, or inhibition of insulin release

Acknowledgement

This study was supported by a grant from the Dutch Stimulation Fund for Research of Aging (SOOM nr. 86-1-205) We thank Sandoz BV, Uden, The Netherlands for generously supplying octreotide.

References

1 Lipsitz LA, Nyqvist RP, Wei JY, Rowe JW Postprandial reduction in blood pressure in the elderly N Engl J Med 1983,309 81-83
2 Jansen RWMM, Lenders JWM, Thien T, Hoefnagels WHL Antihypertensive treatment and postprandial blood pressure reduction in the elderly Gerontology 1987,95 363-368
3 Lipsitz LA, Pluchino FC, Wei JY, Minaker KL, Rowe JW Cardiovascular and norepinephrine responses after meal consumption in elderly (older than 75 years) persons with postprandial hypotension and syncope Am J Cardiol 1986,58 810-815
4 Robertson D, Wade D, Robertson RM Postprandial alterations in cardiovascular hemodynamics in autonomic dysfunctional states Am J Cardiol 1981,48 1048-1052
5 Jansen RWMM, Penterman BJM, van Lier HJJ, Hoefnagels WHL Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin Am J Cardiol 1987,60 1087-1091
6 Jansen RWMM, Hoefnagels WHL Influence of oral and intravenous glucose loading on blood pressure in normotensive and hypertensive elderly subjects J Hypertension 1987,5 S501-S503
7 Rowe JW, Young JB, Minaker KL, Stevens AI , Pallotta JA, I andsberg L Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man Diabetes 1981,30 219-225
8 Christensen NJ Acute effects of insulin on cardiovascular function and noradrenaline uptake and release Diabetologia 1983, 25 377-381
9 Mathias CJ, da Costa DF, Fosbraey P, Christensen NJ, Bannister R Hypotensive and sedative effects of insulin in autonomic failure Br Med J 1987,295 161 163
10 Hoeldtke RD, O'Dorisio ThM, Boden G Treatment of autonomic neuropathy with a somatostatin analogue SMS 201-995 Lancet 1986,II 602-605
11 Williams G, Fuessl H, Kraenzlin M, Bloom SR Postprandial effects of SMS 201-995 on gut hormones and glucose tolerance Scand J Gastroenterol 1986,21(suppl 119) 73-83
12 Wahren J, Eriksson LS The influence of a long acting somatostatin analogue on splanchnic haemodynamics and metabolism in healthy subjects and patients with liver cirrhosis Scand J Gastroenterol 1986,21(suppl 119) 103-108
13 Noseda A, Peeters TI , Delhaye M, Bormans V, Couvreur Y, Vandermoten G, De Francquen P, Rocmans P, Yernault JC Increased plasma motilin concentrations in small cell carcinoma of the lung Thorax 1987,42 784-789
14 Koziol JA, Maxwell DA, Fukushima M, Colmerauer MEM, Pilch YH A distribution-free test for tumor-growth curve analysis with application to an animal tumor immunotherapy experiment Biometrics 1981,37 383-390
15 Said SI Vasoactive peptides Hypertension 1983,5 S17-S26

16. Gribbin B, Pickering TG, Sleight P, Peto R Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 1971,29:424-431.
17. Shimada K, Kitazumi T, Ogura H, Sadakane N, Ozawa T. Differences in age-dependent effects of blood pressure on baroreflex sensitivity between normal and hypertensive subjects. Clin Sci 1986;70:489-494.
18. Domschke S, Domschke W, Bloom SR, Mitznegg P, Mitchell SJ, Lux G, Strunz U. Vasoactive intestinal peptide in man: pharmacokinetics, metabolic and circulatory effects. Gut 1978;19:1049-1053
19. Mitchell SJ, Bloom SR. Measurement of fasting and postprandial plasma VIP in man. Gut 1978;19:1043-1048
20. Sagor GR, Bryant MG, Ghatei MA, Kirk RM, Bloom SR. Release of vasoactive intestinal peptide in the dumping syndrome. Br Med J 1981;282:507-510.
21. Qamar MI, Read AE, Mountford R. Increased superior mesenteric artery blood flow after glucose but not lactulose ingestion. Q J of Med 1986,233:893-896.
22. Norryd C, Dencker H, Lunderquist A, Olin T, Tylén U. Superior mesenteric blood flow during digestion in man. Acta Chir Scand 1975,141:197-202.
23. Eriksson LS, Brundin T, Soderlund C, Wahren J. Haemodynamic effects of a long-acting somatostatin analogue in patients with liver cirrhosis. Scand J Gastroenterol 1987;22·919-925.
24. Wahren J, Felig P. Influence of somatostatin on carbohydrate disposal and absorption in diabetes mellitus. Lancet 1976;II:1213-1216.
25 Schusdziarra V. Somatostatin. A regulatory modulator connecting nutrient entry and metabolism. Horm Metab Res 1980;12:563-577.
26 Brown RT, Polinsky RJ, Lee GK, Deeter JA. Insulin-induced hypotension and neurogenic orthostatic hypotension. Neurology 1986;36:1402-1406.
27 Takata S, Yamamoto M, Yagi S, Nata Y, Ikeda T, Hattori N. Peripheral circulatory effects of insulin in diabetes. Angiology 1985;36·110-116
28. Peeters TL, Janssens J, Vantrappen GR Somatostatin and the interdigestive migrating motor complex in man. Regul Pept 1983;5:209-217
29. Peeters TL, Romanski KW, Janssens J, Vantrappen G. Effect of the long-acting somatostatin analogue SMS 201-995 on small intestinal interdigestive motility in dog. Scand J gastroenterol 1988;23·769-774

CHAPTER VIII

Influence of octreotide (SMS 201-995) and insulin administration on the course of blood pressure after an oral glucose load in hypertensive elderly subjects

R.W.M.M. Jansen, MD, P.H.E.M. de Meijer, MD, H.J.J. van Lier, MSc, W.H.L. Hoefnagels, MD.

Department of Geriatric Medicine, University Hospital Nijmegen, and the Department of Statistical consultation, University of Nijmegen, Nijmegen, The Netherlands.

J Am Geriatr Soc (accepted for publication).

CHAPTER VIII

Influence of octreotide (SMS 201-995) and insulin administration on the course of blood pressure after an oral glucose load in hypertensive elderly subjects

Abstract

Pretreatment with a somatostatin analogue octreotide (SMS 201-995) prevents postprandial blood pressure reduction (BP) in the elderly. We hypothesized that this beneficial effect on BP is caused by an octreotide-induced suppression of insulin secretion. In 10 healthy hypertensive elderly persons (mean age 73 ± 3 years), we studied the effects of octreotide and insulin administration on the course of BP after oral glucose loading. Octreotide was given in a dose of 50 μg sc (time −30 min). Insulin was given sc in a dose of 0.3 U/kg bodyweight (time −10 min) and glucose was given orally in a dose of 75 gram in 300 ml water (time 0 min). Plasma insulin concentrations essentially remained unchanged after placebo and rose to a maximum level of 58 ± 6 mU/l following insulin administration. The course of BP following glucose loading with high or low plasma insulin levels was not different between both tests. These data indicate that the effects of octreotide on postprandial BP reduction in the elderly is unrelated to the inhibition of insulin secretion.

Introduction

It has been demonstrated that blood pressure (BP) in the elderly and in patients with autonomic failure may fall after a meal [1,2,3]. The mechanism of postprandial BP reduction is unknown but it has been proposed that both an impaired sympathetic reflex reactivity to splanchnic vasodilation and interference of insulin with a normal function of the sympathetic nervous system might be responsible [1,4]. The suggestion that insulin plays an important role in postprandial BP reduction is based on the following findings. Firstly, in previous studies we found that BP of elderly persons decreases after oral glucose loading, but not after oral fructose loading [4]. Secondly, preliminary data of our laboratory have shown that BP falls after oral glucose but not after oral fat, protein or water loading. Finally, intravenous insulin has been reported to cause a decrease of BP and even

syncope (not related to hypoglycemia) in diabetic patients and in patients with autonomic failure [5,6,7].
Pretreatment with a somatostatin analogue octreotide (SMS 201-995) completely prevents the fall of BP after oral glucose and we suggested that octreotide may exert this beneficial effect by suppression of insulin secretion [8]. Therefore we designed the present study to investigate the hypothesis that an inhibition of insulin by octreotide can prevent the BP reduction, induced by oral glucose loading, in healthy hypertensive elderly subjects. We studied hypertensive elderly persons since the decrease of BP after an oral glucose load is related to baseline BP [2,4].

Methods

Ten hypertensive elderly subjects (7 men, 3 women) were recruited by a newspaper announcement. Antihypertensive drugs were withdrawn for at least two weeks before the study. The mean age of the subjects was 73 ± 3 (SD) years (range 71 - 81) and the Quetelet index was 26.1 ± 2.6 (SD) kg/m^2. The supine BP after 5 minutes rest measured with a standard sphygmomanometer was 181/99 ± 19/11 (SD) mm Hg. None of the subjects had a history of myocardial infarction, cerebro-vascular accident, congestive heart failure or diabetes mellitus. The study was approved by the local ethical committee and all subjects gave written informed consent.
All studies were carried out in the morning after an overnight fast. During the study the subjects stayed in the supine position. At time 0 min the subjects consumed 75 gram glucose in 300 ml water within 5 minutes. Injections of octreotide, in a dose of 50 μg were given subcutaneously in the upper leg, 10 min before the intake of glucose. Insulin (Actrapid H.M. Penfill® 0.3 U/Kg bodyweight) or placebo (Penfill Test Medium containing phenol 3 mg, glycerol 24 mg and water for injection to 1.5 ml) was injected subcutaneously in the abdomen using an insulin pen (NovoPen®, Novo Industri, Bagsvaerd, Denmark). Injections were given in a randomized order 10 minutes before the glucose load. Oral glucose loading, after insulin or placebo, was performed in each subject with an interval of at least three days.
BP was measured with an automatic recorder (Arteriosonde 1225, Roche) and heart rate was calculated from an ECG-recording at 5 min intervals from −10 to 120 min. Before the injections of octreotide, three BP- and heart rate measurements, taken after 30 min of rest, were averaged and considered as the baseline BP and heart rate. A 21 gauge butterfly needle was inserted 30 min before the start of the test in an antecubital vein and kept patent with a 154 mmol/l NaCl solution. At times −30, −10, 0 and at every 15 min afterwards until time 120 min, blood samples were collected for measurement of glucose and insulin. Blood glucose was estimated using a Reflolux® glucose analyzer (Boehringer Mannheim BV, Almere, The Netherlands), immediately after drawing the blood sample. When

plasma glucose levels fell below 3 mmol/l the test was brought to an end. Plasma glucose values, as given in this study, were measured with an autoanalyzer, using the glucose oxidase method. Plasma insulin was measured in duplicate using a radioimmuno assay.

Statistical comparisons between paired and unpaired observations were made with Student's t-test when appropriate; otherwise Wilcoxon's signed rank and ranked sum tests were used. To reduce the overall probability of a type I error, a level of significance of $p \leq 0.01$ (two-sided) was employed. Comparisons between curves were made with a distribution-free analysis of variance [9]. In this test a p-level of 0.05 or less was considered to be statistically significant. Mean arterial pressure was calculated as the sum of diastolic BP and one third of pulse pressure. All values given in tables and text are expressed as mean ± SEM, unless indicated otherwise.

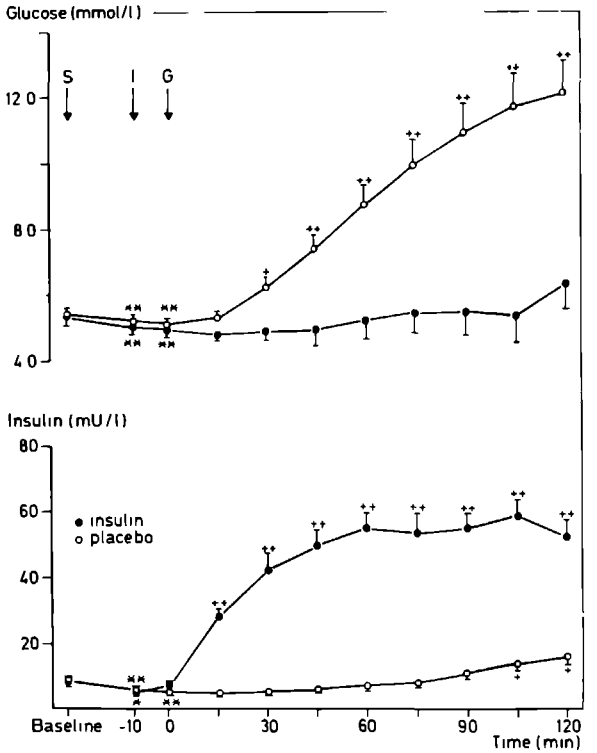

Figure 1 Plasma glucose and insulin levels before and after oral glucose (G). S indicates pretreatment with 50 μg octreotide sc and I insulin or placebo administration

*denotes $p \leq 0.01$ and ** $p \leq 0.001$ when compared with baseline values whereas + means $p \leq 0.01$ and + + means $p \leq 0.001$ compared with values at time 0 min.*

Results

The course of plasma glucose and insulin levels are depicted in Fig 1 In three patients the study with insulin pretreatment was stopped at time 105 min because plasma glucose levels fell below 3 mmol/l Octreotide resulted in a significant decrease of plasma glucose and insulin levels at time −10 and time 0 min After previous placebo administration, oral glucose resulted in a slow rise of plasma glucose with a maximum of 12 1 ± 1 0 mmol/l at time 120 min In contrast, after insulin administration, plasma glucose levels remained unchanged Comparison of the curves of glucose responses revealed a highly significant difference (p=0 006) In the placebo test, octreotide suppressed the insulin response following glucose loading Only at the end of the study period, a slight increase of insulin was found The mean doses of insulin administered was 23 4 ± 1 1 units with a range of 18− 28 After the injection of insulin, plasma insulin concentration increased to 54 ± 6 mU/l at time 60 min with a plateau level until time 120 min Both plasma insulin curves were significantly different (p≤0 001)
Fig 2 represents the course of mean arterial pressure and heart rate after both placebo and insulin administration In both tests BP increased significantly within 20

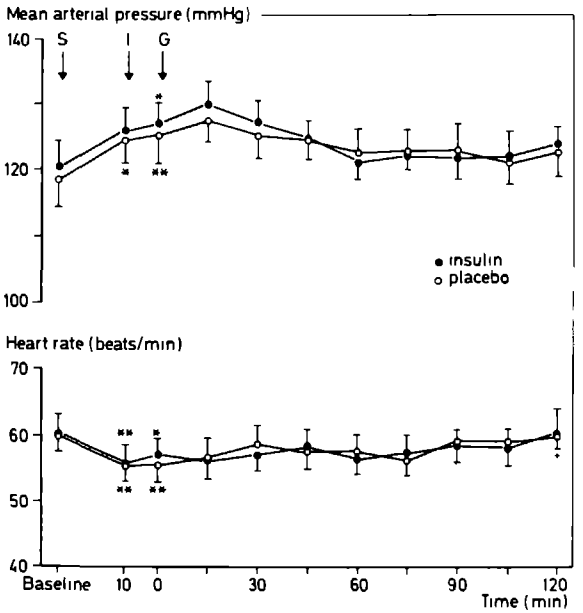

Figure 2 Mean arterial pressure and heart rate before and after oral glucose (G) S indicates pretreatment with 50 μg octreotide sc and I insulin or placebo administration

denotes p≤0 01 and p≤0 001 when compared with baseline values whereas + means p≤0 01 compared with values at time 0 min

min after octreotide administration. Systolic BP increased from 170 ± 7 to 174 ± 7 mm Hg (not significant) before injection of insulin and from 168 ± 7 to 177 ± 6 mm Hg ($p=0.03$) before placebo. Diastolic BP increased from 96 ± 3 to 102 ± 3 mm Hg ($p=0.002$) and from 94 ± 3 to 98 ±4 mm Hg ($p=0.006$), respectively. After the glucose load no change in BP was found in either group. Calculation of the 95% confidence limits demonstrated no difference between the effects of placebo and insulin.

In both tests, heart rate decreased significantly after octreotide, and prior to the glucose load. After the intake of glucose there was a slight increase of heart rate not exceeding baseline levels. In the placebo group, only at time 120 min, the increase of heart rate was significant when compared with the value at time 0 min. No difference between the effects of insulin and placebo was found when comparing the 95% confidence limits.

Discussion

The present study confirms the beneficial effect of octreotide on the fall in BP, induced by oral glucose, in hypertensive elderly subjects. After placebo administration plasma insulin concentrations were significantly suppressed by octreotide whereas, after the injection of insulin, the levels of plasma insulin following oral glucose were comparable to those found previously in the elderly [4,8]. The course of BP was not different between the tests with high or low plasma insulin levels. This clearly demonstrates that the effect of octreotide is unrelated to its inhibition of insulin secretion. Studying two patients with autonomic neuropathy, Hoeldtke et al found that insulin, administered simultaneously with octreotide, prevented postprandial hypotension as effectively as when no insulin was administered [10].

The present study shows that in both test conditions BP increases after octreotide administration. We previously reported that octreotide had no influence on BP and heart rate in normotensive elderly subjects [8], as was also found in young volunteers [11]. Apparently, octreotide has an effect on BP in hypertensive elderly subjects. Furthermore, preliminary data of our laboratory and other studies have demonstrated that BP in patients with autonomic neuropathy also increases after octreotide administration [10,12,13]. A possible explanation for this pressor effect may be its direct vasoconstrictive effect on splanchnic hemodynamics, causing a redistribution of blood flow from the splanchnic to the central circulation [8,14]. On the other hand, octreotide may raise BP by increasing the release of plasma norepinephrine [12]. It can, therefore, be argued that hypertensive elderly and patients with autonomic failure are more sensitive to the pressor effect of octreotide, as was found for a variety of drugs in patients with autonomic neuropathy [15]. During the first period after octreotide administration we found a small but significant decrease of heart rate. To our knowledge no cardio-inhibi-

tory effects of octreotide have been reported. So, the decrease of heart rate may be compensatory to the increase of BP.
One precaution has to be taken into account with respect to the conclusion that suppression of insulin does not contribute to the prevention of BP reduction after octreotide and oral glucose loading. A potentially hypotensive effect of insulin may have been overruled by the pressor effect of octreotide. Insulin may have vasodilating effects. In patients with chronic autonomic failure and in diabetic patients, intravenous insulin administration caused a decrease of BP [5,6,7]. Several studies demonstrated that insulin infusions resulted in a vasodilator effect in dogs and healthy man [16,17,18]. Since in the present study BP curves during high and low plasma insulin levels were similar, an insulin-induced vasodilation, if existing at all, apparently does not play an important role. In addition, in an earlier study we did not find any change in BP after intravenous glucose administration, although plasma insulin concentrations levels were comparable to those found after oral glucose loading [19].
Another explanation for the effect of octreotide on postprandial BP reduction is an inhibition of vasoactive gut hormones, although attempts to identify such a hormone have been unsuccessful [8,10]. Moreover, in a recent study it was demonstrated that in young volunteers superior mesenteric artery blood flow increased to the same extent after carbohydrate, fat and protein meals [20]. These findings suggest that an inhibition of vasoactive gut peptides by octreotide is not involved in its effect on BP.
Although the clinical importance of postprandial hypotension remains to be elucidated, severe dizziness, visual disturbances and syncope simultaneously with large falls in BP were reported [3,21,22,23]. Furthermore, Hoeldtke et al described three patients who were unable to stand after eating [10]. In the elderly and in patients with autonomic failure treatment with octreotide prevents the fall of BP after oral glucose or after meals [8,10]. Therefore, octreotide may be of value in the treatment of symptomatic postprandial hypotension. Caffeine, was also used in the treatment of postprandial hypotension [24,25] but the pressor effect of caffeine was not as consistently effective as octreotide [10].
In conclusion, our data indicate that in hypertensive elderly subjects BP does not change after an oral glucose loading test with pretreatment of octreotide and insulin. The beneficial effects of octreotide on postprandial hypotension therefore seems unrelated to its suppression of insulin release.

Acknowledgement

We thank Sandoz BV, Uden, The Netherlands for generously supplying octreotide.

References

1 Lipsitz LA, Nyqvist RP, Wei JY, Rowe JW Postprandial reduction in blood pressure in the elderly N I ngl J Med 1983,309 81-83

2 Jansen RWMM, Lenders JWM, Thien T, Hoefnagels WHL Antihypertensive treatment and postprandial blood pressure reduction in the elderly Gerontology 1987,95 363-368

3 Robertson D, Wade D, Robertson RM Postprandial alterations in cardiovascular hemodynamics in autonomic dysfunctional states Am J Cardiol 1981,48 1048-1052

4 Jansen RWMM, Penterman BJM, van Lier HJJ, Hoefnagels WHL Blood pressure reduction after oral glucose loading and its relation to age, blood pressure and insulin Am J Cardiol 1987,60 1087-1091

5 Mathias CJ, da Costa DF, Fosbraey P, Christensen NJ, Bannister R Hypotensive and sedative effects of insulin in autonomic failure Br Med J 1987,295 161-163

6 Brown RT, Polinsky RJ, Lee GK, Deeter JA Insulin-induced hypotension and neurogenic orthostatic hypotension Neurology 1986,36 1402-1406

7 Takata S, Yamamoto M, Yagi S, Nata Y, Ikeda T, Hattori N Peripheral circulatory effects of insulin in diabetes Angiology 1985,36 110-116

8 Jansen RWMM, Peeters I L, Lenders JWM, van Lier HJJ, van 't Laar A, Hoefnagels WHL Somatostatin analogue octreotide (SMS 201-995) prevents the decrease of blood pressure after oral glucose loading in the elderly J Clin Endocrinol Metab 1989,68 752-756

9 Koziol JA, Maxwell DA, Fukushima M, Colmerauer MEM, Pilch YH A distribution-free test for tumor-growth curve analysis with application to an animal tumor immunotherapy experiment Biometrics 1981,37 383-390

10 Hoeldtke RD, O'Dorisio ThM, Boden G Treatment of autonomic neuropathy with a somatostatin analogue SMS 201-995 Lancet 1986, II 602-605

11 Eriksson I S, Brundin T, Soderlund C, Wahren J Haemodynamic effects of a long-acting somatostatin analogue in patients with liver cirrhosis Scand J Gastroenterol 1987,22 919-925

12 Dudl RJ, Anderson DS, Forsythe AB, Ziegler MG, O'Dorisio TM Treatment of diabetic diarrhea and orthostatic hypotension with somatostatin analogue SMS 201-995 Am J Med 1987,83 584-588

13 Hoeldtke RD, Boden G, O'Dorisio TM Treatment of postprandial hypotension with a somatostatin analogue (SMS 201 995) Am J Med 1986,81(suppl 6B) 83-87

14 Wahren J, Friksson LS The influence of a long-acting somatostatin analogue on splanchnic haemodynamics and metabolism in healthy subjects and patients with liver cirrhosis Scand J Gastroenterol 1986,21(suppl 119) 103 108

15 Bannister R, Davies B, Holly E, Rosenthal T, Sever P Defective cardiovascular reflexes and supersensitivity to sympathicomimetic drugs in autonomic failure Brain 1979,102 163 176

16 Liang C-S, Doherty JU, Fallace R, Maekawa K, Arnold S, Gavras H, Hood WB Insulin infusions in conscious dogs Effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines J Clin Invest 1982,69 1321 1336

17 Reikeras O, Gunnes P Effects of high doses of insulin on regional blood flows during acute left ventricular failure in dogs European Heart J 1986,7 992-998

18 Creager MA, Liang CS, Coffman JD Beta adrenergic-mediated vasodilator response to insulin in the human forearm J Pharmacol Exp Ther 1985,235 709 714

19 Jansen RWMM, Hoefnagels WHL Influence of oral and intravenous glucose loading on blood pressure in normotensive and hypertensive elderly subjects J Hypertension 1987,5 S501-S503

20 Qamar MI, Read AE Effects of ingestion of carbohydrate, fat, protein, and water on the mesenteric blood flow in man Scand J Gastroenterol 1988,23 26-30

21 Seyer-Hansen K Postprandial hypotension Br Med J 1977,2 1262

22 Lipsitz LA, Pluchino FC, Wei JY, Minaker KL, Rowe JW Cardiovascular and norepinephrine responses after meal consumption in elderly (older than 75 years) persons with postprandial hypotension and syncope Am J Cardiol 1986,58 810-815
23 Hoeldtke RD, O'Dorisio TM, Boden G Prevention of postprandial hypotension with somatostatin Ann Intern Med 1985,103 889-890
24 Onrot J, Goldberg MR, Biaggioni I, Hollister AS, Kincaid D, Robertson D Hemodynamic and humoral effects of caffeine in autonomic failure Therapeutic implications for postprandial hypotension N Engl J Med 1985,313 549-554
25 Lenders JWM, Morre HLC, Smits P, Thien Th The effects of caffeine on the postprandial fall of blood pressure in the elderly Age Ageing 1988,17 236-240

Summary

Postprandial blood pressure reduction in the elderly has not yet been studied extensively. After the first report of Lipsitz et al in 1983, which demonstrated that in institutionalized ill elderly subjects on chronic medication systolic blood pressure may decline after a meal, Westenend et al reported that a fall in blood pressure after a meal can also be found in healthy, community-dwelling elderly persons. In this group systolic blood pressure decreased by 7% and diastolic blood pressure by 14% at 50 minutes after the start of a breakfast. The occurrence of postprandial blood pressure reduction in healthy elderly subjects was subsequently confirmed by Lipsitz et al. In young healthy normotensive subjects blood pressure remained essentially unchanged after a meal.

In the first place we investigated whether treatment with antihypertensive drugs may cause an increase in the postprandial blood pressure reduction in the elderly. An exaggerated fall might be expected from an interference of antihypertensive medication with blood pressure homeostasis. In chapter I, however, we report that elderly hypertensive patients treated with diuretics, β-blockers, vasodilators or a combination of these drugs, have a similar postprandial blood pressure reduction as hypertensive elderly without medication. In chapter II we demonstrate that antihypertensive treatment with nitrendipine, a new long-acting calcium antagonist, or hydrochlorothiazide may even improve blood pressure homeostasis after a meal. In this study we used an oral glucose load instead of a meal in order to determine not only postprandial blood pressure reduction but also the effects of both treatments on carbohydrate metabolism. After 12 weeks of treatment with both drugs, the percentage changes of mean arterial pressure at 60 minutes after the glucose load (when the maximal decline in blood pressure was found) were significantly smaller in both groups when compared with pretreatment values.

The mechanism of postprandial blood pressure reduction in the elderly is unknown, but an important role for carbohydrates and insulin was proposed by Lipsitz et al. They suggested that an age-related decrease of insulin-induced sympathetic nervous system activation may in part be responsible for postprandial hypotension. Failure of sympathetic nervous system activation was proposed to be mediated by blunting of baroreflex sensitivity by insulin or glucose. To elucidate the role of insulin in postprandial hypotension we studied the effects of oral glucose and oral fructose loading on blood pressure in chapter III. In contrast to an isocaloric, isosmotic and isovolumic glucose load, ingestion of fructose elicited only a small increase in plasma glucose and insulin levels. After glucose loading,

mean arterial pressure decreased by 17 mm Hg in hypertensive elderly and by 6 mm Hg in normotensive elderly subjects whereas after oral fructose loading blood pressure did not change in both groups. The fall in blood pressure after oral glucose starts about 15 minutes after ingestion and reaches its maximum within about 60 minutes. The magnitude and time course of the blood pressure reduction in normotensive and hypertensive elderly subjects after 75 gram of glucose are as much alike as those found after a breakfast containing 49 gram of carbohydrates, 1.8 gram of fat and 13.4 gram of proteins, as was used in the study described in chapter I. These findings give support to the suggestion that the blood pressure reduction after a meal is related to glucose.

In chapter IV we determined whether the hypotensive effects of glucose loading is specifically mediated by gastrointestinal factors or by vasodilator properties of insulin. In this study we compared the effects of oral versus intravenous glucose loading in normotensive and hypertensive old subjects and found that only oral glucose loading lowered blood pressure in both groups. After oral glucose loading mean arterial pressure fell by 16 mm Hg in the hypertensives and by 8 mm Hg in the old normotensives. These data indicate that it is unlikely that a vasodilator effect of insulin primarily determines the fall in blood pressure after oral glucose.

Chapter V describes the results of a study to determine the effects of oral glucose loading on baroreflex sensitivity. It has been suggested that eating may affect blood pressure homeostasis through an insulin-induced blunting of baroreflex sensitivity. In this study we continously measured blood pressure in the finger by the Finapres, a new non-invasive blood pressure device. Baroreflex sensitivity, as measured by the phenylephrine and nitroglycerin methods, is diminished in the elderly, especially in hypertensive elderly subjects. However, glucose loading had no influence on baroreflex sensitivity. So we concluded that a further decrease of baroreflex function in response to glucose and/or insulin is not involved in the etiology of postprandial blood pressure reduction.
The magnitude of the reduction in mean arterial pressure after the glucose load is almost twice as high in the hypertensive elderly as in normotensive elderly persons (chapter III, IV and VII). In addition, in the aforementioned studies, a weak but significant relation is found between baseline blood pressure and the reduction in mean arterial pressure. This relation is in accordance with the decrease of baroreflex sensitivity related to age and blood pressure, as was found in chapter V.

In order to determine whether not only glucose but also other nutrients may interfere with postprandial blood pressure homeostasis, we designed a study to investigate the effects of glucose, fat, protein and water loading on blood pressure in healthy hypertensive elderly subjects (chapter VI). In this study we found that blood pressure fell only after oral glucose loading while oral fat, protein and water loading had no influence on blood pressure. These results and the findings of

chapter III and IV, in which we found that blood pressure only fell after oral glucose, but not after oral fructose or intravenous glucose loading, suggest that oral glucose induces a specific splanchnic or systemic vasodilation, possibly mediated by vasoactive gastrointestinal hormones.

The secretion of gastrointestinal hormones (but also of insulin) can be suppressed by a long-acting somatostatin analogue, octreotide (SMS 201-995). In chapter VII we studied the effects of octreotide on the blood pressure reduction in normotensive and hypertensive subjects aged 70 years or older, after oral glucose in relation to plasma concentrations of vasoactive intestinal polypeptide (VIP) and insulin. We found that a single subcutaneous injection of octreotide, in a dose of 50 μg, completely prevents the fall of BP after oral glucose in both groups. Octreotide had no effect on plasma VIP concentrations before or after glucose loading. In chapter VI we found a significant increase of somatostatin following fat and protein loading, whereas VIP only increased after fat loading, however, without a concomitant decrease of blood pressure. Therefore, we conclude that the data on VIP make clear that this peptide does not play an important role in the postprandial blood pressure reduction. However, this does not exclude a role for other vasoactive gut hormones such as neurotensin, substance P or bradykinin.

Other explanations for the effects of octreotide on postprandial blood pressure are a suppression of insulin release, as was found in chapter VII, or a vasoconstrictive action on splanchnic hemodynamics. To elucidate the role of insulin, we investigated the effects of octreotide administration together with insulin or placebo, on the course of blood pressure after oral glucose loading in ten hypertensive elderly persons in chapter VIII. Insulin was given subcutaneously in a dose 0.3 U/kg bodyweight and resulted in a mean maximum plasma insulin level of 58 mU/L. However, the course of blood pressure following oral glucose with high or low plasma insulin levels was not different between both tests, which indicates that the effect of octreotide on postprandial blood pressure reduction in the elderly is unrelated to the inhibition of insulin secretion.

The cause of postprandial blood pressure reduction remains unresolved. The decrease of blood pressure after a meal seems to be related to the ingestion of glucose, but whether vasoactive gut hormones or other glucose related factors such as insulin play a causal role, remains open for debate. It is of genuine importance to determine superior mesenteric artery blood flow after different nutrients in the elderly, since it has been found in young volunteers that superior mesenteric artery blood flow increases to the same extent after carbohydrate, fat and protein meals.
The effects of the loading tests on sympathetic nervous system activity can be derived from changes in plasma norepinephrine. In this study, plasma norepinephrine rose significantly after oral glucose loading and may therefore reflect

activation of the sympathetic nervous system elicited by the fall in blood pressure. The increases of plasma norepinephrine in hypertensive elderly subjects were equal to or lower than the increases of plasma norepinephrine in normotensive old and young subjects, despite a greater fall in blood pressure. This is in accordance with the decrease of baroreflex sensitivity related by age and blood pressure. However, in normotensive elderly subjects, we also found an increase of plasma norepinephrine after oral fructose and intravenous glucose loading, while blood pressure remained unchanged. The similar increase of plasma norepinephrine, both after oral glucose and fructose loading, indicates that an impairment of an insulin-mediated sympathetic nervous system activation does not play an important role in postprandial blood pressure reduction in the elderly, as was suggested before. In addition to fructose and intravenous glucose loading, ingestion of a fat solution, in hypertensive elderly persons, induced increases of plasma norepinephrine, comparable to those found after glucose loading. We conclude, therefore, that the activation of the sympathetic nervous system does not only occur as a response to the fall in blood pressure. Non-specific stimuli from the gastrointestinal tract may also contribute to the degree of sympathetic nervous system activation.

In conclusion, blood pressure in the elderly may fall after a meal. Antihypertensive treatment may reduce the postprandial fall in blood pressure. Although the mechanism is not fully understood, postprandial blood pressure reduction seems to be related to glucose related factors, since blood pressure only falls after oral glucose loading, but not after oral fructose, fat or protein loading. Vasoactive gastrointestinal hormones may play a role in the glucose induced vasodilation of splanchnic vasculature, but attempts to identify such hormones were unsuccessful. Therefore we suggest that interference of insulin with a sympathetic response diminished by age or desease to splanchnic vasodilation, may be responsible for the postprandial fall in blood pressure in the elderly. However, vasodilator effects of insulin or a baroreflex response diminished by insulin do not seem to be involved. Finally, the clinical significance of postprandial blood pressure reduction in the elderly, for instance as a cause of falling, remains to be elucidated.

Samenvatting

Postprandiale bloeddrukdaling bij bejaarden is tot op heden nog nauwelijks onderzocht. Na het eerste artikel van Lipsitz e.a. in 1983, waarin beschreven werd dat bij geïnstitutionaliseerde zieke bejaarden die chronisch medicatie gebruikten, de systolische bloeddruk na een maaltijd kan dalen, beschreef Westenend e.a. dat ook bij gezonde bejaarde proefpersonen de bloeddruk na een maaltijd dalen kan. In deze groep daalde de gemiddelde systolische bloeddruk met 7% en de diastolische bloeddruk met 14% op 50 minuten na aanvang van een ontbijt. Het vóórkomen van postprandiale bloeddrukdaling bij gezonde bejaarden werd vervolgens bevestigd door Lipsitz e.a.. Bij gezonde jonge vrijwilligers bleef de bloeddruk na een maaltijd nagenoeg onveranderd.

Als eerste werd onderzocht of bij bejaarden, die behandeld werden met antihypertensieve medicatie, een grotere daling van de bloeddruk na een maaltijd zou optreden. Een grotere daling zou verwacht kunnen worden op grond van interferentie van antihypertensiva met de bloeddrukregulatie. In hoofdstuk I wordt echter beschreven dat bij bejaarde hypertensie patiënten die behandeld worden met diuretica, beta-blokkers, vaatverwijders of een combinatie van deze middelen, een vergelijkbare postprandiale bloeddrukdaling optreedt als bij hypertensieve bejaarden zonder behandeling met medicijnen. In hoofdstuk II wordt aangetoond dat antihypertensieve behandeling met nitrendipine, een nieuwe, lang werkende calcium antagonist, of hydrochloorthiazide de bloeddrukregulatie na een maaltijd zelfs kan doen verbeteren. In deze studie gebruikten wij in plaats van een maaltijd een orale glucosebelasting om naast de postprandiale bloeddrukdaling ook de effecten van beide behandelingen op het koolhydraat metabolisme vast te stellen. Na 12 weken behandeling met elk van beide medicamenten waren de procentuele veranderingen van de gemiddelde arteriële bloeddruk op 60 minuten na inname van de glucoseoplossing (het tijdstip waarop de maximale bloeddrukdalingen werden gemeten) in beide groepen significant lager dan vóór behandeling.

De oorzaak van de postprandiale bloeddrukdaling bij bejaarden is niet bekend, maar door Lipsitz e.a. werd gesuggereerd dat glucose en insuline een belangrijke rol spelen. Zij veronderstelden dat een leeftijdsafhankelijke vermindering van een door insuline geïnduceerde stimulatie van het sympatische zenuwstelsel voor een gedeelte de postprandiale hypotensie zou kunnen veroorzaken. Vermindering van de activering van het sympatische zenuwstelsel zou worden veroorzaakt door een verminderde gevoeligheid van de baroreflex ten gevolge van insuline of glucose. Om de rol van insuline in de postprandiale hypotensie nader te bestuderen werden in hoofdstuk III de effecten van een orale glucose- en een orale fructose-

belasting op de bloeddruk onderzocht In tegenstelling tot een glucoseoplossing, veroorzaakt inname van een fructoseoplossing, met een gelijk volume en een gelijke calorische en osmotische waarde, slechts een geringe stijging van de plasma glucose en insuline spiegels Na de glucosebelasting daalde de gemiddelde arteriele bloeddruk met 17 mm Hg in de groep van hypertensieve bejaarden en met 6 mm Hg in de groep van normotensieve bejaarden, terwijl de orale fructose belasting geen invloed op de bloeddruk had De daling in bloeddruk na de glucosebelasting trad al na 15 minuten na inname van de glucoseoplossing in en bereikt het maximum na ongeveer 60 minuten. De grootte en tijdsduur van de postprandiale bloeddrukdaling na een glucosebelasting was zowel bij normotensieve als hypertensieve bejaarden ongeveer gelijk aan de bloeddrukdaling na een ontbijt bestaande uit 49 gram koolhydraten, 1,8 gram vet en 13,4 gram eiwit, zoals gebruikt in de studie beschreven in hoofdstuk I Deze bevindingen ondersteunen de suggestie dat de bloeddrukdaling na een maaltijd gerelateerd is aan glucose

In hoofdstuk IV is onderzocht of de hypotensieve effecten van een glucosebelasting veroorzaakt worden door maagdarm factoren of door vaatverwijdende eigenschappen van de insuline In deze studie werden de effecten van een orale en een intraveneuze gluosebelasting vergeleken bij normotensieve en hypertensieve ouderen Alleen een orale glucosebelasting resulteerde in beide groepen in een bloeddrukdaling terwijl de bloeddruk niet veranderde na een intraveneuze glucosebelasting Na de orale glucosebelasting daalde de gemiddelde arteriele bloeddruk met 16 mm Hg bij de hypertensieve bejaarden en met 8 mm Hg bij de normotensieve bejaarden Deze gegevens wijzen erop dat een vaatverwijdend effect van insuline waarschijnlijk niet de oorzaak is van de bloeddrukdaling na een orale glucosebelasting

In hoofdstuk V worden de resultaten beschreven van een studie waarin de effecten van een orale glucosebelasting op de baroreflex gevoeligheid onderzocht zijn Er is gesuggereerd dat voedselopname de bloeddrukregulatie zou beinvloeden door een door insuline geinduceerde verminderde gevoeligheid van de baroreflex In deze studie werd de bloeddruk continu gemeten aan de vinger met behulp van de Finapres, een nieuw, niet invasief bloeddrukapparaat De baroreflex gevoeligheid, bepaald met behulp van de phenylephrine en nitroglycerine methode, was volgens verwachting bij bejaarden verminderd, met name bij bejaarden met een verhoogde bloeddruk Echter, de glucosebelasting had geen invloed op de baroreflex gevoeligheid Derhalve kan geconcludeerd worden dat een verminderde functie van de baroreflex ten gevolge van glucose en/of insuline geen etiologische rol van betekenis speelt bij postprandiale bloeddrukdaling.
De daling van de gemiddelde arteriele bloeddruk na de glucosebelasting is bij hypertensieve bejaarden ongeveer twee keer zo groot als bij normotensieve bejaarden (hoofdstuk III, IV en VII) Bovendien wordt er in de reeds eerder genoemde studies een significante relatie gevonden tussen de uitgangsbloeddruk

en de daling van de gemiddelde arteriële bloeddruk. Deze relatie komt overeen met de door leeftijd en bloeddruk verminderde baroreflex gevoeligheid zoals die gevonden werd in hoofdstuk V.

Om vast te stellen of naast glucose ook andere nutriënten een invloed hebben op de postprandiale bloeddrukregulatie werden de effecten van glucose, vet, eiwit en water op de bloeddruk bestudeerd bij gezonde, hypertensive, bejaarde proefpersonen (hoofdstuk VI). Alleen na glucose daalde de bloeddruk terwijl vet, eiwit en water geen effect hadden op de bloeddruk. Deze resultaten, alsmede de bevindingen uit eerdere studies (hoofdstuk III, IV en VII), waarin werd aangetoond dat de bloeddruk alleen daalde na orale glucose maar niet na intraveneuze glucose of orale fructose toediening, wijzen erop dat glucose een specifieke vaatverwijding induceert in het maagdarm vaatbed of systemische vaatbed. Mogelijk wordt deze vaatverwijding bewerkstelligd door vasoactieve maagdarm hormonen.

De afscheiding van maagdarm hormonen, maar ook van insuline, kan worden onderdrukt door de langwerkende somatostatine analoog octreotide (SMS 201-995). In hoofdstuk VII werden bij vrijwilligers van 70 jaar of ouder met een normale of verhoogde bloeddruk de effecten van octreotide op de bloeddrukdaling na een orale glucosebelasting bestudeerd, in relatie tot de plasma spiegels van VIP en insuline. In deze studie bleek dat door een eenmalige onderhuidse toediening van 50 μ octreotide de bloeddrukdaling na de glucosebelasting in beide groepen volledig kon worden voorkomen. Octreotide had vóór noch ná de glucosebelasting enig effect op de plasma VIP concentraties. In hoofdstuk VI werd een significante stijging van somatostatine gevonden na een vet en eiwit belasting terwijl VIP alleen steeg na een vet belasting, echter zonder een gelijktijdige daling van de bloeddruk. Concluderend kan gesteld worden dat VIP geen belangrijke rol speelt bij de postprandiale bloeddrukdaling. Echter, dit sluit niet uit dat andere vasoactieve hormonen, zoals substantie P, neurotensine of bradykinine mogelijk een rol kunnen spelen.

Andere verklaringen voor de effecten van octreotide op de postprandiale bloeddrukdaling zijn een onderdrukking van de insuline secretie en een constrictie van de arteriën in het maagdarm gebied. Om de rol van insuline nader te bestuderen werden in hoofdstuk VIII de effecten bestudeerd van octreotide, met gelijktijdige toediening van insuline of placebo, op het verloop van de bloeddruk na een orale glucosebelasting bij 10 hypertensieve bejaarde vrijwilligers. Insuline werd subcutaan gegeven in een dosering van 0.3 U/kg lichaamsgewicht. Dit resulteerde in een gemiddelde, maximale, plasma insuline spiegel van 58 mU/l. Het verloop van de bloeddruk na een orale glucosebelasting was echter niet verschillend tussen de test met een lage en de test met een hoge insuline spiegel. Dit wijst erop dat het effect van octreotide op de postprandiale bloeddrukdaling bij bejaarden niet verklaard kan worden door remming van de insuline secretie.

De oorzaak van de postprandiale bloeddrukdaling blijft onopgelost. De daling van de bloeddruk na een maaltijd lijkt gerelateerd te zijn aan de inname van glucose maar of vasoactieve darm hormonen of aan glucose gerelateerde factoren, zoals insuline, een causale rol spelen, blijft ter discussie staan. Het is van belang bij bejaarden de bloeddoorstroming te bepalen van de arteria mesenterica superior na inname van verschillende nutriënten omdat bij jonge vrijwilligers is aangetoond dat de bloeddoorstroming van de arteria mesenterica superior in gelijke mate toeneemt na koolhydraat, vet en eiwit maaltijden.

De effecten van de belastingtesten op de activiteit van het sympatische zenuwstelsel kunnen worden afgeleid van de veranderingen in de plasma noradrenaline concentraties. In onze studies (hoofdstuk III, IV, V and VI) steeg het plasma noradrenaline significant na de orale glucosebelasting en dit kan derhalve een afspiegeling zijn van een activering van het sympatische zenuwstelsel ten gevolge van de daling in bloeddruk. De toename van het plasma noradrenaline bij de hypertensieve bejaarden vrijwilligers was gelijk aan of lager dan de toename van noradrenaline bij de normotensieve bejaarde en jonge vrijwilligers, ondanks een grotere daling in bloeddruk. Dit is in overeenstemming met de door leeftijd en bloeddruk verminderde baroreflex gevoeligheid. Bij de normotensieve bejaarde vrijwilligers werd er tevens een stijging van het plasma noradrenaline gevonden na een orale fructose en een intraveneuze glucosebelasting, ondanks het gegeven dat de bloeddruk onveranderd bleef. De gelijke stijging van plasma noradrenaline na zowel een orale glucose- als een orale fructosebelasting, wijst erop dat een door insuline bewerkstelligde verminderde activering van het sympatische zenuwstelsel geen belangrijke rol speelt in de postprandiale bloeddrukdaling bij bejaarden zoals eerder gesuggereerd was. Bovendien veroorzaakt een vet oplossing bij hypertensieve bejaarde vrijwilligers een stijging van plasma noradrenaline vergelijkbaar met een stijging na een orale glucosebelasting.
Derhalve kan geconcludeerd worden dat de activering van het sympatische zenuwstelsel niet alleen veroorzaakt wordt door de daling van de bloeddruk. Aspecifieke stimuli van het maagdarm systeem kunnen ook bijdragen tot de activering van het sympatische zenuwstelsel.

Concluderend kan men stellen dat de bloeddruk bij bejaarden na een maaltijd kan dalen. Wellicht dat antihypertensieve medicatie de postprandiale bloeddrukdaling kan verminderen. Hoewel het mechanisme niet volledig bekend is, lijkt de postprandiale bloeddrukdaling gerelateerd te zijn aan glucose gezien het feit dat de bloeddruk wel na een glucosebelasting maar niet na een orale fructose, vet of eiwit belasting daalt. Vasoactieve maagdarm hormonen kunnen een rol spelen in de door glucose geïnduceerde vaatverwijding in het maagdarm gebied, hoewel er geen dergelijk hormoon geïdentificeerd kon worden. Het lijkt waarschijnlijk dat interferentie van insuline met een door leeftijd en ziekte verminderde activering van het sympatische zenuwstelsel op de vaatverwijding in het maagdarm gebied

een rol speelt in de postprandiale bloeddrukdaling bij bejaarden. Echter, vaatverwijdende effecten van insuline of een door insuline verminderde gevoeligheid van de baroreflex gevoeligheid spelen waarschijnlijk geen rol. De klinische relevantie van de postprandiale bloeddrukdaling bij bejaarden, b.v. als oorzaak voor het vallen, dient onderzocht te worden.

Dankwoord

Velen hebben aan de totstandkoming van dit proefschrift bijgedragen waarvoor ik hen allen hartelijk wil danken
Allereerst de proefpersonen die, vaak meermaals, aan het onderzoek hun medewerking verleenden en veel geslikt hebben, ook al was dit niet altijd even smaakvol Theo Thien en Jacques Lenders hebben de aanzet gegeven tot dit onderzoek Ik ben hun zeer erkentelijk voor de begeleiding van het eerste gedeelte van het onderzoek (hoofdstuk 1) In het kader van een wetenschappelijke stage heeft Berry Penterman bijgedragen aan het onderzoek beschreven in hoofstuk 3 Met veel inzet was Joeke Reyenga te allen tijde bereid haar medewerking te verlenen wanneer nodig Rob Hermsen en Jacques Willemsen van het laboratorium voor Experimentele en Chemische Endocrinologie (Hoofd Prof Dr Th J Benraad) verrichtte nauwgezet de bepalingen van, respectievelijk, insuline en catecholaminen De plasmaspiegels van VIP en somatostatine werden bepaald door medewerkers van het laboratorium voor Gastrointestinale hormonen, Katholieke Universiteit te Leuven, België (Hoofd Prof Dr T L Peeters) Ir Henk van Lier van de Mathematisch Statistische Advies afdeling ben ik dankbaar voor het bewerken van de gegevens Lex Sewuster van de afdeling MIV/SDA zorgde voor verschillende computer programma's Van Dr J Lennis en de verpleegkundigen van de polikliniek voor Inwendige Geneeskunde kreeg ik de gelegenheid om de verschillende experimenten uit te voeren De meeste tekeningen in dit proefschrift werden met zorg gemaakt door Cees Nicolasen van de afdeling Medische Illustratie en gefotografeerd door de medewerkers van de afdeling Medische Fotografie Mevr L van 't Laar-Langerveld was behulpzaam om in korte tijd tekeningen te vervaardigen Riky Lamers zorgde voor de maaltijden en de verschillende test oplossingen Anky Verweyen, Louise Jagtenberg en Ans Ruesen hebben met zorg verschillende artikelen getypt Cees Groenewoud was behulpzaam bij het corrigeren van de Engelse tekst Tenslotte wil ik alle leden van de hypertensiegroep bedanken voor de vele vruchtbare discussies

Curriculum vitae

René Jansen, geboren op 24 december 1956 te Apeldoorn, behaalde in 1978 het diploma laboratoriumopleiding HBO-A, Klinische Chemie te Deventer. Na het behalen van het colloquium doctum in september 1978 te Nijmegen, begon hij in dezelfde maand, met zijn studie geneeskunde aan de Katholieke Universiteit te Nijmegen, waar hij in 1985 het artsexamen aflegde. Van januari 1986 tot januari 1989 was hij werkzaam als arts-onderzoeker, eerst op de afdeling algemeen inwendige geneeskunde (Hoofd: Prof. Dr. A. van 't Laar) en later op de afdeling geriatrie (Hoofd: Dr. W.H.L. Hoefnagels) van het St. Radboudziekenhuis te Nijmegen. Sinds 1 februari 1989 is hij in opleiding tot internist in het St. Radboudziekenhuis (opleider: Prof. Dr. A. van 't Laar).

Stellingen

behorende bij het proefschrift

MEALS AND BLOOD PRESSURE IN THE ELDERLY

Experimental studies on postprandial blood pressure reduction

René Jansen

Nijmegen, 2 juni 1989

1. Postprandiale bloeddrukdaling is specifiek gerelateerd aan inname van glucose. Dit wijst erop dat insuline een belangrijke rol speelt in de pathofysiologie van dit phenomeen.

Dit proefschrift

2. Bij symptomatische postprandiale bloeddrukdaling is een behandeling met octreotide (SMS 201-995) te overwegen.

Dit proefschrift

3. Voor een goede beoordeling van het effect van antihypertensieve medicatie bij ouderen moet de invloed van de maaltijd worden geëlimineerd.

Dit proefschrift

4. De hypothese dat een abnormale secretie van somatostatine na een orale glucose belasting bij ouderen een verklaring kan zijn voor de postprandiale bloeddrukdaling, dient nader te worden onderzocht.

Dit proefschrift

5. Orthostatische hypotensie bij ouderen mag nooit uitsluitend aan de leeftijd worden toegeschreven.

Sl Mader et al. JAMA 1987;258:1511-1514

6. Voordat de conclusie getrokken kan worden dat de bepaling van dopamine-betahydroxylase een eenvoudige en betrouwbare laboratoriumproef is om familiaire middellandse-zeekoorts aan te tonen dient eerst onderzoek verricht te worden bij controlegroepen.

MH Barakat et al. Lancet 1988;II:1280-1283

7. Het ontbreken van anemie of macrocytose is geen reden om een onderzoek naar vitamine B12 deficientie achterwege te laten.

J Lindenbaum et al. N Engl J Med 1988;318:1720-1728

8. Bij ouderen hebben thiazidediuretica geen invloed op de cholesterol en triglyceride concentraties in het plasma.

RWMM Jansen et al. Clin Pharmacol Ther 1989;45:291-298

9. De communicatie tussen artsen en patiënten zou er mee gebaat zijn als artsen zouden beseffen dat de meeste patiënten niet langer dan twee minuten het woord voeren, althans wanneer men ze zonder interrupties rustig laat uitspreken over hun klachten.

JN Blau. Br Med J 1989;298:39

10. Het vermogen om zelfstandig beslissingen te nemen neemt niet noodzakelijkerwijs af met de leeftijd.

JA Barondess et al. J Am Geriatr Soc 1988;36:919-937

11. Wie zegt dat een kunstwerk te snel gemaakt is, heeft misschien te snel gekeken.

Vincent van Gogh, 26-05-1888

12. Alleen wanneer de te drinken glucoseoplossing ijs- maar dan ook ijskoud is vindt er bij ouderen geen bloeddrukdaling plaats.

H Kuipers, RWMM Jansen, WHL Hoefnagels, eigen waarneming

13. Uit de "citation index" van stellingen uit proefschriften in het dagblad NRC-Handelsblad valt af te leiden dat het met de creativiteit van Nijmeegse onderzoekers droevig gesteld is.

14. In de subsidie-aanvraag voor een onderzoeksproject dient een royaal reisbudget te worden opgenomen.

ISBN 90-9002885-4